Prescribing patterns of biologic immunomodulating medicine in the South African private health care sector

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ABSTRACT

Title: Prescribing patterns of biologic immunomodulating medicine in the South African private health care sector.

Keywords: biologics, biologic immunomodulating medicine, biological medicine, autoimmune diseases, rheumatoid arthritis, multiple sclerosis, Crohn's disease, pharmacoeconomics, drug utilisation review.

Advances in molecular immunology and rapid technical evolution during the past two decades have led to a new class of medicines called biologics. Recently, a large number of biologics, or biologic immunomodulators, directed towards an array of immune-mediated diseases, have entered the market. This has lead to a dramatic change in the immunotherapy of autoimmune diseases, as biologics present new potential to improve or substitute conventional immunosuppressive therapies. According to literature, biologics are used by only a small number of a health plan's members, (approximately one per cent), but a single occurrence can be relatively expensive. Furthermore, there is an indication that the frequency of use and cost of biologics are on the rise, and as more biologics enter the market, health plans and employers face the challenge of controlling costs while ensuring that biologics are affordable.

The general objective of this study was to determine the prevalence and cost of biologic immunomodulating medicine in the treatment of certain autoimmune diseases during the period 2005 to 2008 in a section of the private health care sector of South Africa, by employing a medicine claims database as a source to obtain necessary information.

A quantitative, retrospective drug utilisation review (rDUR) was performed on computerised medication records (medicine claims data) for four consecutive years (i.e. 2005 to 2008) provided by a pharmacy benefit management company (PBM). The study population consisted of all patients on the database who received at least one medicine item with adalimumab, etanercept, infliximab, interferon beta-1a, interferon 1-b or rituximab as active ingredient and who were diagnosed with either rheumatoid arthritis (RA), multiple sclerosis (MS) or Crohn's disease between 1 January 2005 and 31 December 2008.

Between 2005 and 2008, an average of 1,305,201 patients appeared on the total database, and of these 0.055% (n = 713) received biologic immunomodulating medicine. More than two thirds of biological users were female and most patients who received these medicine items were between the ages of 39 and 64 years, followed by those patients aged between 25 and

39 years. Biologic immunomodulating medicine items (n = 11,914) and biologic prescriptions (n = 9,537) represented 0.016% of the total number of medicine items (N = 76,129,173) and 0.030% of the total number of prescriptions (N = 31,985,153). The percentage contribution of biologic immunomodulators to the total number of medicine items and prescriptions on the total database increased each year, and in four years' time the percentage of all the medicine items on the total database that included biologic immunomodulators had tripled, from 0.009% to 0.023%.

The total cost of biologic immunomodulating medicine accounted for 1.278% of the total cost (N = R7, 483,759,176.23) of all medication claimed through the PBM between 2005 and 2008. The percentage contribution of biologic immunomodulators to the total medicine expenditure also increased from one year to another for the four-year study period. The average cost of a biologic immunomodulating medicine item increased with 71.10% from 2005 (R5602.71 ± 2166.61) to (R9586.25 ± 5956.56) in 2008. The CPI for biologic immunomodulators, (CPI = 60.00 for 2005; CPI = 74.62.17 for 2006; CPI = 85.26 for 2007; and CPI = 86.96 for 2008) indicated that biologic immunomodulating medicine items were relatively expensive and the *d*-value between the average cost per biologic immunomodulator and the average cost per non-biological medicine item (*d*-value = 2.54 in 2005, *d*-value = 3.32 in 2006, *d*-value = 2.23 in 2007 and *d*-value = 1.59 in 2008) furthermore indicated that the impact of biological therapies was large and practically significant.

Rheumatoid arthritis patients represented 19.78% of the total number of patients (n = 713) who claimed the biologic immunomodulators during the four-year period, MS patients (n = 172) represented 24.12% and Crohn's patients (n = 11) represented 1.5%. Biological drugs prescribed to RA patients represented 0.28% (n = R20, 708,818.82) of the total cost (N = R7, 483,759,176.23) of all medication claimed through the PBM during the four-year period, while those prescribed to MS patients represented 0.41% (R30, 922,520.07) and those prescribed to Crohn's disease patients represented 0.015% (R1, 108,568.02).

Although biologic immunomodulating medicine items used in the treatment of RA, MS and Crohn's disease are relatively expensive, it seems that the number of other medication prescribed to patients with these diseases decreased after treatment with biologics, which may influence the medicine treatment cost of these patients.

It can be concluded that even though biologic immunomodulators are used by only a very small percentage of the total patient population in a section of the private health care sector of South Africa, they are relatively expensive and have a considerable impact not only the medical aid scheme, but also on the patient.

OPSOMMING

Titel: Voorskryfpatrone van biologiese immunomodulerende medisyne in die Suid-Afrikaanse privaat gesondheidsorgsektor.

Sleutelwoorde: biologiese produkte, biologiese immunomodulerende medisyne, biologiese medisyne, outo-immuun siektes, rumatoïde artritis, veelvuldige sklerose, Crohn se siekte, farmako-ekonomie, medisyneverbruiksevaluering.

Vooruitgang in molekulêre immunologie en 'n vinnige tegnologiese ontwikkeling gedurende die afgelope twee dekades het 'n nuwe groep geneesmiddels, bekend as biologiese produkte, opgelewer. 'n Groot aantal biologiese produkte, of biologiese immunomoduleerders, wat gemik is op 'n verskeidenheid van immuunbemiddelde siektetoestande het onlangs die medisynemark bereik. Dit het aanleiding gegee tot 'n ingrypende verandering in immunoterapie van outo-immuun siektes, aangesien biologiese produkte nuwe potensiaal bied om konvensionele immuun-onderdrukkende terapieë te verbeter of te vervang. Volgens die literatuur word biologiese produkte gebruik deur slegs 'n klein gedeelte van 'n mediese fonds se lede (ongeveer een persent), maar 'n enkele voorval kan relatief duur wees. Boonop is daar 'n aanduiding dat die frekwensie van gebruik, sowel as die koste van biologiese produkte, besig is om te styg en soos wat nuwe biologiese produkte die mark bereik, word mediese fondse en werkgewers gekonfronteer met die uitdaging om die koste van hierdie produkte te beheer terwyl hulle moet verseker dat dit bekostigbaar is.

Die algemene doel van hierdie studie was om die voorkoms en koste van biologiese immunomodulerende medisyne in die behandeling van sekere outo-immuun siektes in 'n gedeelte van die privaat gesondheidsorgsektor van Suid-Afrika te bepaal vir die periode 2005 tot 2008 deur gebruik te maak van 'n medisyne-eis databasis as 'n bron om die nodige inligting te bekom.

Die navorsingsmetode wat gebruik is in hierdie studie was 'n kwantitatiewe, retrospektiewe medisyneverbruiksevaluering. Data was verkry vanaf gerekenariseerde medisyne rekords (medisyne-eis data) vir vier opeenvolgende jare (2005 tot 2008) wat beskikbaar gestel was deur 'n apteek voordelebestuursmaatskappy. Die studie populasie het bestaan uit al die pasiënte op die databasis wat ten minste een medisyne item ontvang het wat adalimumab, etanercept, infliximab, interferon beta-1a, interferon 1-b of rituximab as aktiewe bestanddeel gehad het en wat gediagnoseer is met rumatoïde artritis (RA), veelvuldige sklerose (VS) of Crohn se siekte tussen 1 Januarie 2005 en 31 Desember 2008.

Tussen 2005 en 2008 het daar ’n gemiddeld van 1,305,201 pasiënte op die totale databasis verskyn, waarvan 0.055% (n = 713) biologiese immunomodulerende medisyne ontvang het. Meer as twee derdes van die pasiënte wat biologiese produkte gebruik het was vroulik en meeste van die pasiënte was tussen die ouderdomme van 39 en 64 jaar, gevolg deur pasiënte tussen die ouderdomme van 25 en 39 jaar. Biologiese immunomodulerende medisyne items (n = 11,914) en biologiese voorskrifte (n = 9,537) het 0.016% van die totale aantal medisyne items (N = 76,129,173) en 0.030% van die totale aantal voorskrifte (N = 31,985,153) verteenwoordig. Die persentasie van die totale aantal medisyne items en voorskrifte op die totale databasis wat deur biologiese immunomodulerende medisyne verteenwoordig is, het elke jaar verhoog. In vier jaar se tyd het die persentasie van al die medisyne items op die totale databasis, wat verteenwoordig is deur biologiese immunomoduleerders, verdriedubbel vanaf 0.009% tot 0.023%.

Die totale koste van biologiese immunomodulerende medisyne was verantwoordelik vir 1.278% van die totale koste (N = R7, 483,759,176.23) van al die medikasie wat geëis is deur die apteek voordelebestuursmaatskappy tussen 2005 en 2008. Die persentasie bydrae van biologiese immunomoduleerders tot die totale medisyne uitgawes het ook verhoog van een jaar na die volgende gedurende die vier-jaar periode. Die gemiddelde koste van ‘n biologiese immunomodulerende medisyne item het met 71.10% verhoog vanaf (R5602.71 ± 2166.61) in 2005 na (R9586.25 ± 5956.56) in 2008. Die koste-voorkoms indeks (“CPI”: *Cost-prevalence index*) vir biologiese immunomoduleerders, (CPI = 60.00 vir 2005; CPI = 74.62.17 vir 2006; CPI = 85.26 vir 2007; en CPI = 86.96 vir 2008) het aangetoon dat biologiese immunomodulerende medisyne items relatief duur was. Die *d*-waarde tussen die gemiddelde koste per biologiese immunomoduleerder en die gemiddelde koste per nie-biologiese medisyne item (*d*-waarde = 2.54 in 2005, *d*- waarde = 3.32 in 2006, *d*- waarde = 2.23 in 2007 en *d*- waarde = 1.59 in 2008) het boonop aangetoon dat die impak van biologiese terapieë groot en prakties betekenisvol was.

Pasiënte met RA het 19.78% van die totale aantal pasiënte (n = 713) verteenwoordig wat biologiese immunomoduleerders geëis het gedurende die vier-jaar periode. Pasiënte met VS (n = 172) het 24.12% verteenwoordig en pasiënte met Crohn se siekte (n = 11) het 1.5% verteenwoordig. Biologiese medisyne wat voorgeskryf is vir pasiënte met RA het 0.28% (n = R20, 708,818.82) van die totale koste (N = R7, 483,759,176.23) van alle medikasie wat deur die apteek voordelebestuursmaatskappy geëis is tussen 2005 en 2008 verteenwoordig. Biologiese medisyne wat voorgeskryf is vir pasiënte met VS het 0.41% (R30, 922,520.07) verteenwoordig en die wat voorgeskryf is vir pasiënte met Crohn se siekte het 0.015% (R1, 108,568.02) verteenwoordig.

Alhoewel die biologiese immunomodulerende medisyne wat gebruik word in die behandeling van RA, VS en Crohn se siekte relatief duur is, blyk dit of die aantal ander medisyne items wat voorgeskryf word vir pasiënte met hierdie siektetoestande afneem nadat hulle met biologiese produkte behandel is. Die medisyne behandelingskoste van hierdie pasiënte mag hierdeur beïnvloed word.

Die gevolgtrekking kan gemaak word dat, alhoewel biologiese immunomoduleerders deur slegs 'n klein gedeelte van die totale pasiënt populasie in 'n gedeelte van die privaat gesondheidsorg sektor van Suid-Afrika gebruik word, is hierdie middels relatief duur en het hulle 'n aansienlike uitwerking op beide mediese fondse en pasiënte as betalers.

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LIST OF ABBREVIATIONS

Ab	*antibody*[6]
ADCC	*antibody-dependant cell-mediated cytotoxicity*[6]
Ag	*antigen*[6]
AICAR	*aminoimidazole carboxamide ribonucleotide*[6]
AIDS	*acquired immunodeficiency syndrome*[6]
APC	*antigen-presenting cells*[6]
AS	*ankylosing spondylitis*[6]
ASA	*aminosalicylic acid*[6]
ATC	*Anatomical Therapeutic Chemical*[10]
BCR	*B-cell receptor*[6]
BFAC	*Biologic Finance and Access Council*[8]
CBER	*Center for Biologics Evaluation and Research*[2]
CD	*cluster of differentiation*[6]
CDER	*Center for Drug Evaluation and Research*[2]
CMS	*Council for Medical Schemes*[1]
CNDM	*congenital nasolacrimal duct mucocele*[6]
CNS	*central nervous system*[6]
COX	*cyclooxygenase*[6]
CRP	*C-reactive protein*[6]

CSF	*colony stimulating factor*[6]
CTLA-4	*Cytotoxic T-Lymphocyte Antigen-4*[6]
DHFR	*dihydrofolate reductase*[6]
DMARD	*disease modifying anti-rheumatic drug*[6]
DUR	*drug utilisation review*[7]
FCAS	*familial cold autoinflammatory syndrome*[6]
FDA	*Food and Drug Administration*[2]
FDC	*Food, Drug, and Cosmetic*[2]
G-CSF	*granulocyte colony-stimulating factor*[6]
GI	*gastro-intestinal*[6]
GIT	*gastro-intestinal tract*[6]
GM-CSF	*granulocyte-macrophage colony-stimulating factor*[6]
HAQ	*Health Assessment Questionnaire*[4]
hGH	*human growth hormone*[6]
HIV	*human immunodefiency virus*[6]
HLA	*human leukocyte antigen*[6]
ICAM	*inter-cellular adhesion molecule*[6]
ICD-10	*International Classification of Diseases 10th revision*[11]
IFN	*interferon*[6]
Ig	*immunoglobulin*[6]
IL	*interleukin*[6]

IM	*intramuscular*[6]
IMS	*Information Management System*[3]
ITP	*idiopathic thrombocytopenic purpura*[6]
IV	*intravenous*[6]
JRA	*juvenile rheumatoid arthritis*[6]
LFA	*leukocyte functional antigen*[6]
MCC	*Medicines Control Council*[5]
MCO	*Managed Care Organisation*[8]
MHC	*major histocompatibility complex*[6]
MIMS	*Monthly Index of Medical Specialities*[9]
MS	*multiple sclerosis*[6]
MTX	*methotrexate*[6]
NK	*natural killer*[6]
NSAID	*nonsteroidal anti-inflammatory drug*[6]
PBM	*Prescribed Minimum Benefit*[1]
Ps	*psoriasis*[6]
PsA	*psoriatic arthritis*[6]
RA	*rheumatoid arthritis*[6]
rDUR	*retrospective drug utilisation review*[7]
RF	*rheumatoid factor*[6]
SC	*subcutaneous*[6]

SDAI	*Simplified Disease Activity Index*[4]
SSRI	*selective serotonin reuptake inhibitors*[6]
Tc	*cytotoxic T cell*[4]
TCR	*T-cell receptor*[4]
TGF	*Transforming growth factor*[1] *OR Tumor growth factor*[6]
Th	*helper T cell*[4]
TNF	*tumor necrosis factor*[6]
UC	*ulcerative colitis*[6]
VCAM	*vascular cell adhesion molecule*[6]
WBC	*white blood cell*[6]
WHO	*World Health Organization*[10]

[1]Council for Medical Schemes, 2005; [2]FDA, 2009a; [3]IMS, 2009; [4]Mayer, 2009a; [5]Medicines Control Council, 2008; [6]Myers, 2006; [7]Perez, 2001; [8]Peskin, 2008; [9]Snyman, 2009; [10]WHO, 2009; [11]WHO, 2010.

LIST OF SYNONYMS

biologic immunomodulating medicine	*biologic immunomodulators*
	biologic immunotherapeutics
biologics	*biological medicine*
	biological products
	biological treatments
	biological therapies
	biotherapeutics
	biopharmaceuticals
	biotech drugs

CHAPTER 1

Introduction

Chapter one reflects on the general layout of this dissertation. It includes the background and motivation for the study, research questions and research objectives as well as the research method. The chapter concludes with the division of chapters.

1.1 Background and motivation for the study

During the past 10 to 15 years there has been a dramatic change in the immunotherapy of autoimmune diseases (Nepom, 2002:812), as advances in molecular immunology and rapid technical evolution have led to a new class of medicines called biologics (Van Eden *et al.*, 2009:1).

Biologics, also referred to as biological medicine, are defined in various ways, depending on who is using the term (Goff *et al*., 2008:14). Webster *et al*. (2003) state that biologics have been defined in dissimilar terms, depending on the scientific, regulatory, or legal context, and verify that no comprehensive and universally precise definition exists. As a group, biologics are often referred to as biopharmaceuticals, targeted therapies, specialty pharmaceuticals, and high-cost, high-maintenance drugs (Goff *et al*., 2008:14), although in general this class of medicine is typically bundled under the designation of "biologic" or "immunotherapies". However, according to Huges and Hann (2007:1), biologics do not represent a homogeneous group of drugs, and a single term therefore does not do justice to the diversity within this therapeutic group.

Goff *et al*. (2008:14) regard a good working definition of biologics as "*drugs made from living organisms and genetically engineered to produce specific therapeutics"*, whereas Webster *et al*. (2003) define a biologic as "*a prophylactic, an in vivo diagnostic, or a therapeutic substance that can be made only by a living system and that has a large, complex, inherently heterogeneous molecular structure*". Huges and Hann (2007:1) simply state that biologics

are by definition *"proteins and/or derivatives thereof that modulate the immune system, down-regulate the inflammatory response or support tumor specific defenses"*.

Katz (2006) explains that it should come as no surprise that there are as many diverse definitions for biologics, as medical and legal definitions of the term "biologic" vary markedly. He adds that the focus typically falls on one or more of three considerations, namely

- mechanism of action;
- side-effect profile; and
- molecular structure, but argues that these distinctions are not clinically meaningful.

In the search for a comprehensive and explicit definition for the term "biologics" for the purpose of this study, it became clear that such a definition is difficult to find. However, even though various functional definitions for biologics subsist, there is at least one universal decisive factor that applies throughout for these products: any product that is termed a "biologic" or "biological product" has to be approved and licensed by the US Food and Drug Administration (FDA) as such (FDA, 2008:1). The significance of the role of the FDA lies in the fact that virtually all of the original biologics available for use in humans today (and *all* the biologics relevant to this study) were developed and manufactured by American pharmaceutical companies, that in most cases still hold the patents on these products. The Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) within the FDA has been regulating biological products in the United States since September 2002 (Sanbar, 2004:171). Only when these products are approved and licensed for use by the FDA, can they be exported to and registered in other countries around the world.

The South African Medicines Control Council (MCC) registers biologics for use in South Africa, and according to the MCC, biological medicines can be defined largely by preference to their method of manufacture – the biological process (Medicines Control Council, 2008). The definitions provided by both the MCC and the FDA will thus be considered as the operational definitions of biologics for the purpose of this study:

The MCC defines biological medicine as *"a medicine where the active ingredient and/or key exipients have been derived from living organisms or tissues, or manufactured using a biological process*" (Medicines Control Council, 2008), whereas the FDA defines biological products (biologics) as being "*products that replicate natural substances such as enzymes, antibodies, or hormones in the human body*" (FDA, 2008:2).

Therefore, throughout this dissertation, a "biologic" or "biological product" is regarded as a prophylactic, an *in vivo* diagnostic or therapeutic substance that

- is produced only by a living system, but is not simply a metabolite;
- is stated to contain a single substance that has documented biological activity;
- has a relatively large molecular weight with a high structural complexity;
- is inherently heterogeneous in the molecular species present and has an impurity profile that depends critically upon the processes used to make and test each batch;
- has activity that is often very sensitive to physical conditions (temperature, shear forces, phase) and enzymatic action; and/or
- usually requires bioassays for batch release and stability assessment, rather than chemical tests for identity and purity (Webster *et al*., 2003).

Biologics presently on the market are designed to treat cancers, rare diseases like Gaucher disease, and a few hard-to-treat chronic conditions, such as intestinal disorders, psoriasis, multiple sclerosis, and rheumatoid arthritis (Goff *et al*., 2008:14). Many biologics have been designed to modulate a specific aspect of the primary autoimmune process, thus avoiding generalised immunosuppression (Isaacs *et al.,* 1999:S121). Also referred to as biologic response modifiers (BRMs) or immunomodulating agents, these biologics are often employed in biological therapy or "biotherapy" (Isaacs *et al*., 1999:121).

Biological therapy is defined as *"treatment to stimulate or restore the ability of the immune system to fight infection and disease"* (National Cancer institute, 2009). Biological therapy is therefore any form of treatment that uses the body's natural abilities that comprise the immune system to fight infection and disease or to guard the body from some of the side-effects of treatment. The human body generally produces low levels of BRMs in response to infection and disease, but BRMs can be made in large numbers in the laboratory to treat cancer, rheumatoid arthritis, and other diseases (National Cancer institute, 2009). Forms of BRMs include monoclonal antibodies, interferon, interleukin-2 (IL-2), and various types of colony- stimulating factors (CSF, GM-CSF, G-CSF) (Nepom, 2005:813).

In recent years a large number of biologic immune modifiers, or biologic immunomodulators, directed towards an array of immune-mediated diseases entered the market (Kong *et al*., 2006). This has led to a dramatic change in the immunotherapy of autoimmune diseases,

because of the new potential to improve or substitute conventional immunosuppressive therapies (Nepom, 2002:812). Table 1.1 (adapted from Nepom, 2002:813) presents a list of recent biologics with clinical efficacy in autoimmunity.

Table 1.1 Recent biologics with efficacy in clinical autoimmunity (Nepom, 2002:813)

Compounds	Target	Available in SA*
Infliximab, etanercept, onercept	TNFα	YES (Revellex®), YES ((Enbrel®), NO.
Daclizumab, basiliximab	CD25 (IL-2 receptor)	NO, YES (Simulect®).
Alemtuzumab	CD52	YES (Mabcampath®).
Alefacept	CD2	NO.
Efalizumab	CDIIa (LFA-1)	NO.
Natalizumab	VLA-4	NO.
Rituximab	CD20	YES (Mabthera®).
Epratuzumab	CD22	NO.
Glutiramer acetate	TCR-MHC interaction	NO.
MHC, major histocompatibility complex; TCR, T cell receptor; CD, cluster of differentiation		
***Snyman, 2010:363 – 401.**		

According to Goff *et al*. (2008:14), biologics are only used by a small number of a health plan's members, (approximately one per cent), but a single occurrence can be relatively expensive. According to a South African Pharmaceutical Benefit Manager (PBM), Mediscor (Pty) Ltd, the biological medicine Enbrel® reached position 50 on their top 50 products ranked according to contribution to total medicine expenditure for 2007 (Bester & Hammann, 2008:13), which is significant when considering that it was ranked 99th in 2005 and 84th in 2006. This might be an indication that the frequency of use and/or the cost of biologics is on the rise, and as more biologics enter the market, health plans and employers face the challenge of controlling costs while ensuring that biologics are affordable (Goff *et al.*, 2008).

Johnston (2006:342) states that biological medicines are relatively expensive to develop and also subject to the essential processes of costly and time consuming clinical trials. Furthermore, even though biological therapies are effective, they mostly require continuous administration and have undesirable side-effects (Van Eden *et al.*, 2009:1). Therefore, when biological medicines have been approved and licensed for use, they are relatively expensive to utilise. This is why cost is a significant consideration when deciding whether to use these products and careful patient and disease selection are so crucial (Johnston, 2006:342).

Peskin (2008:1), a commercial and medicare health plan medical director for the Chatham Institute, states that the emergence of biological therapies is straining traditional models of health insurance and health care financing. He adds that biologic therapies and personalised medicine add another dimension of complexity to the challenges today's managed care decision makers face. He explains this by stating that biologics offer benefits for improved quality of life for the patients that use them. On the other hand, however, for the payers and purchasers of medicine, the cost of biologics is triggering changes in the benefit design of medical aid schemes that include the shifting of medication costs to patients, as well as attempts to control or limit the cost of these therapeutics (Peskin, 2008:1).

Goff *et al*. (2008:2) agree that the cost burden associated with health care is being shifted from payers and purchasers to patients in response to accelerating health care costs. This has created access barriers, above all for biologic therapies, for which the cost burden can be sizeable, but the potential benefits associated with these therapies warrant examination in the context of health care coverage, financing, access and administration. The unintended consequences of limiting access and reimbursement for biologics could reverse well-meaning attempts to control unnecessary health care resource utilisation, and to reduce total health care expenditures (Goff *et al*., 2008:2).

Against this background it is clear that research should be conducted with regard to the impact of novel biologic immunomodulators on medicine usage and cost in South Africa.

On the basis of the preceding discussion the following research question can be formulated:

- What are the prescribing patterns of biologic immunomodulating medicine in the treatment of certain autoimmune diseases (especially rheumatoid arthritis, multiple sclerosis and Crohn's disease) in South Africa?

1.2 Research objectives

The research objectives are divided into general and specific research objectives.

1.2.1 General research objective

The general objective of this research project was to investigate the prescribing patterns of biological medicines in the treatment of certain autoimmune diseases, and the costs associated with such patterns, in a section of the private health care sector of South Africa.

1.2.2 Specific research objectives

The specific objectives consist of two phases, namely a literature review and an empirical investigation. The following aims need to be achieved from each of the phases respectively:

1.2.2.1 Phase 1: Literature review

The specific research objectives of the literature review include the following:

- Conceptualise the immune system, its responses and components involved in the pathogenesis of autoimmune diseases from available literature.
- Conceptualise "biologics" from available literature.
- Conceptualise the usage patterns of biologics in South Africa from available literature.
- Investigate the use of biologics in the treatment of autoimmune diseases, while focusing on rheumatoid arthritis, multiple sclerosis and Crohn's disease, and determine the pre-usage requirements (i.e. prescribing guidelines and protocols) of biologics in these diseases.
- Conceptualise the economic impact of biologics on the cost of health care and investigate the legislation surrounding the payment of biologics and the issues regarding generic biologics.

1.2.2.2 Phase 2: Empirical investigation

The specific research objectives of the empirical investigation included the following:

With regard to biologic immunomodulators in general:

- Analyse the current prescribing patterns and cost trends of biologic immunomodulators in a section of the private health care sector of South Africa by using a medicine claims database for the period 2005 to 2008.
- Analyse how biologic immunomodulators influence medicine expenditure of medical aid schemes in a section of the private health care sector of South Africa over time.

With regard to biologic immunomodulators specifically used in the treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease:

- Determine the prescribing patterns of biologic immunomodulators in the treatment of rheumatoid arthritis, multiple sclerosis or Crohn's disease.
- Determine the cost of biologic immunomodulators and how it compares with the cost of other medication (excluding biologics) received by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease.
- Investigate the influence of biologic immunomodulators on the prescribing patterns of other medication (excluding biologics) after treatment with biologics in patients with rheumatoid arthritis, multiple sclerosis and Crohn's disease.

1.3 Research methods

The research methods were divided into a literature phase and an empirical phase.

1.3.1 Literature phase

The following steps will be followed in the literature phase: (i) understand the immune system and autoimmune diseases from available literature and the protocols for the treatment of the diseases with special focus on novel biologic drugs, and (ii) determine current prevalence of the use of biologic drugs for diseases of the immune system and the economic impact of biologics on the cost of national and global health care.

1.3.2 Empirical phase

A retrospective drug utilisation study was done on data provided by a medicine claims database, while focusing on the period from 1 January 2005 to 31 December 2008.

1.3.2.1 Data source and study population

The database used in this study was provided by a pharmacy benefit management (PBM) company that manages the benefits of medical schemes and –insurance companies in South Africa. This type of organisation provides real-time auditing processes to claims from pharmacies and other service providers. By 2009, the company provided pharmaceutical benefit management services to 38 medical schemes, and between 2005 and 2008, 31,985,153 prescriptions and 76,129,173 medicine items with a total cost of R7, 483 759 176.23 had been claimed through the PBM.

An eleven digit reference number on each prescription record linked each patient, medical practice, pharmacy or medical scheme to line items, and a “dummy” member number was allocated by the PBM to each patient to ensure patient confidentiality.

Other information available on the database included: (1) dispensing date of prescription, (2) trade names and active ingredients of medicine items, (3) NAPPI codes, (4) NAPPI code extension and description, (5) number of medicine items prescribed, (6) final prescription cost, (7) total cost paid by the medical scheme and patient, (8) patient’s date of birth, (9) patient’s gender, (10) prescriber type and (11) provider type.

1.3.2.2 Research design

The research question and objectives were conceived and studied using data that had been collected and recorded between 2005 and 2008. The research design of this research project was therefore a retrospective drug utilisation review (refer to section 3.2.1).

1.3.2.3 Descriptive measures

Various elements were identified against which medicine items and prescriptions could be measured. These measures included *prevalence*, *prescribing patterns* and *total cost* and are explained in chapter three.

1.3.2.4 Data analysis

Research data were analysed by using the Statistical Analysis System® for Windows 9.1 (SAS 9.1®). Microsoft Excel® and Microsoft Word® were also used to illustrate various results of the analysed data through tables and graphs.

1.3.2.5 Reliability and validity of data

Research data were directly obtained from the PBM and no manipulations were done by the researcher. Data were furthermore tested for outliers and random data checks were conducted. Research was thus done with the assumption that data were reliable and valid.

1.3.2.6 Ethical considerations

Permission to conduct this study was obtained from the board of directors of the PBM as well as the ethical committee of the North-West University. (Ethical application number: NWU-0046-08-S5).

1.4 Division of chapters

Chapter 1: Introduction

Chapter 2: An overview of the immune system and biologic immunotherapeutic medicine

Chapter 3: Empirical investigation

Chapter 4: Results and discussion

Chapter 5: Conclusions and recommendations

1.5 Chapter summary

This chapter reflected on the background and the motivation for this study, research questions, research objectives, research methods, and an outline of the literature review and the empirical investigation. Chapter two will encompass a literature review regarding various aspects of the immune system and biological medicine.

CHAPTER 2

An overview of the immune system and biological medicine

Chapter two includes an overview of the biology of the immune system as well as the prevalence, indications and clinical effects of biological medicine. The chapter also includes a discussion on the pharmacoeconomic aspects of biological medicine.

2 Introduction

Agents that improve or modify the balance of different components of the immune system are fast becoming imperative in the management of various chronic and life-threatening diseases, including certain autoimmune diseases (Lake *et al.*, 2004:931). The use of these agents is increasing at enormous rates as new classes, new agents, and new indications of current immunotherapeutic agents are continually being developed (Beers, 2006:1329). One such new class is a group of agents called biologics, or biologic immunomodulators. Although the mechanisms of action of most of these agents are still unclear, an understanding of the components of the immune system could be useful in understanding these agents' effects (Lake *et al*., 2004:931).

This section discusses the biology of the immune system and focuses on the immune responses and components involved in the pathogenesis of various autoimmune diseases.

2.1 The immune system

The immune system is an organisation of cells and molecules with specialised tasks to guard against infection (Delves & Roitt, 2000:37). This complex system is designed to protect the host from invading pathogens and to eliminate disease through a series of defences (Male, 2003:7). All the components of the immune system work together through immune

responses which may be normal or abnormal. Normal immune responses have desirable consequences, such as defending and healing the body, but unfortunately immune responses can also be deviant and yield undesirable consequences that cause harm to the body (Figure 2.1). Both normal and abnormal immune responses will be discussed in the following sections.

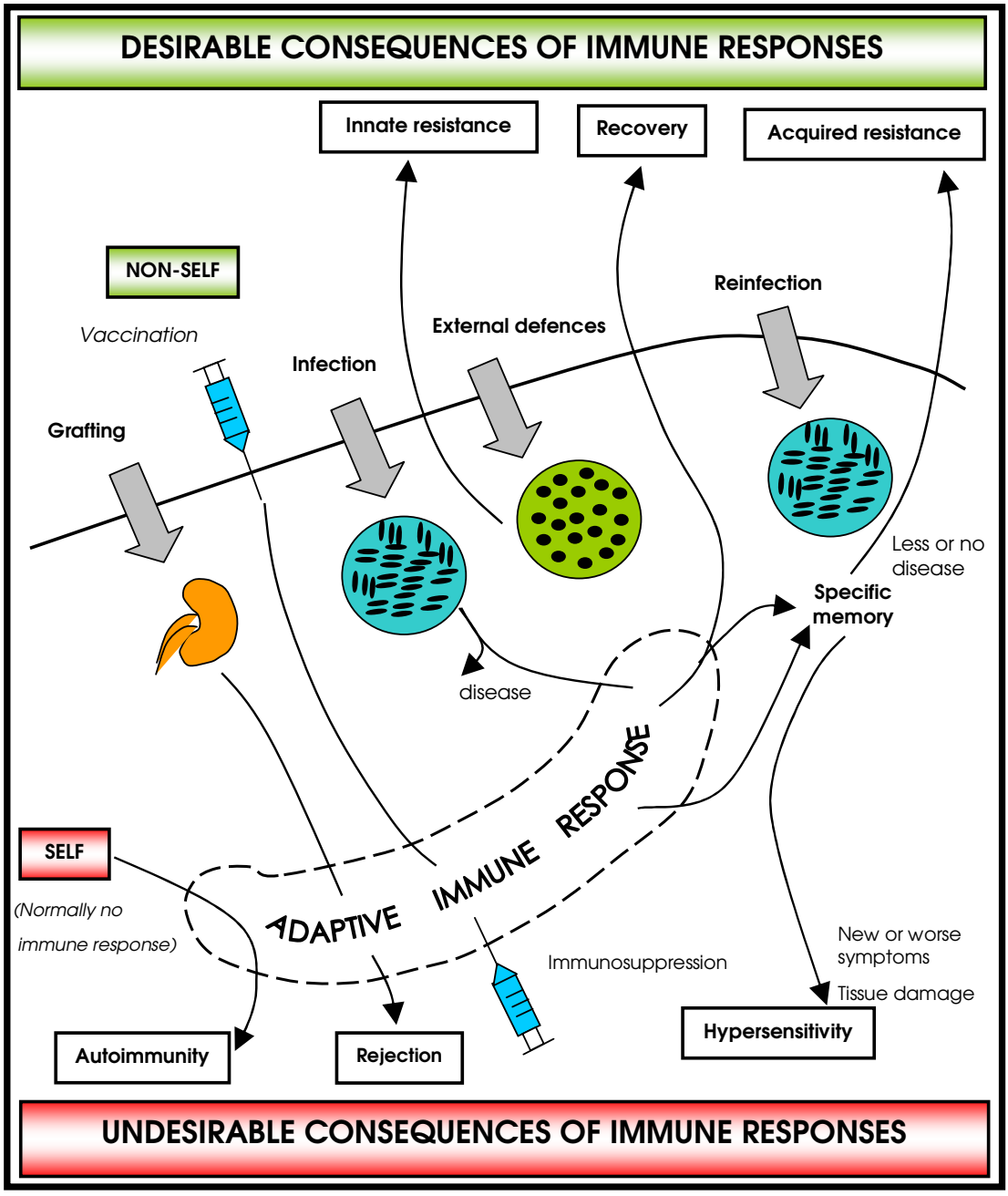

Figure 2.1 Desirable and undesirable consequences of immunity (Adapted from Playfair and Chain, 2005:8)

2.2 Normal immune responses

The body's first line of defence against invading pathogens are mechanical or physical barriers, that include the skin, cornea of the eyes and mucosa of the respiratory, gastrointestinal, and genito-urinary tracts. As long as these barriers remain intact, many pathogens cannot enter the body, but breaching of any of these barriers sets off the next line of defence, that involves certain white blood cells (leucocytes) that move through the bloodstream and into tissues, searching for and attacking infectious agents. This defence is called immunity and has two parts: innate and adaptive immunity (Elgert, 2009:15).

The body is likely to react to nearly anything that can be bound by the receptors of either the innate or the adaptive immune system (Delves & Roitt, 2000:37). Any such molecule capable of being recognised by the immune system is defined by Pinchuk (2000:2) as an antigen (Ag). The immune system can direct specific responses against a wide range of antigens to protect the host from infection or disease (Johnston, 2006:337).

At its functioning best, the immune system is accurately responsive to invading pathogens while maintaining the ability to distinguish "self" antigens to which it is tolerant (Doan *et al*., 2005:3). When the immune system distinguishes self molecules from non-self molecules, potentially harmful non-self molecules and cells are eliminated from the body. Abnormal cells that originate from host tissues can also be recognised and destroyed (Doan *et al*., 2005:3).

The immune system can make this distinction because all cells carry a set of distinctive proteins on their surface. This set of unique markers on human cells is collectively known as human leukocyte antigens (HLA), or the major histocompatibility complex (MHC) (Chapel, 2006:3). Each person has an almost unique combination of human leukocyte antigens that is normally recognised by his/her immune system as "self" antigens (Todd & Spickett, 2005:20). Immune cells generally do not attack "self" antigens, that all carry the same pattern of self-markers; rather, the immune system coexists peacefully with other host cells in a state known as self-tolerance (Pathak & Palan, 2005:4). HLA molecules can, however, provoke an immune response in another host and are therefore referred to as antigens (Todd & Spickett, 2005:20).

Figure 2.2 is an illustration of the HLA molecules on the surface of human cells, collectively known as the major histocompatibility complex (Schindler *et al*., 2005:3).

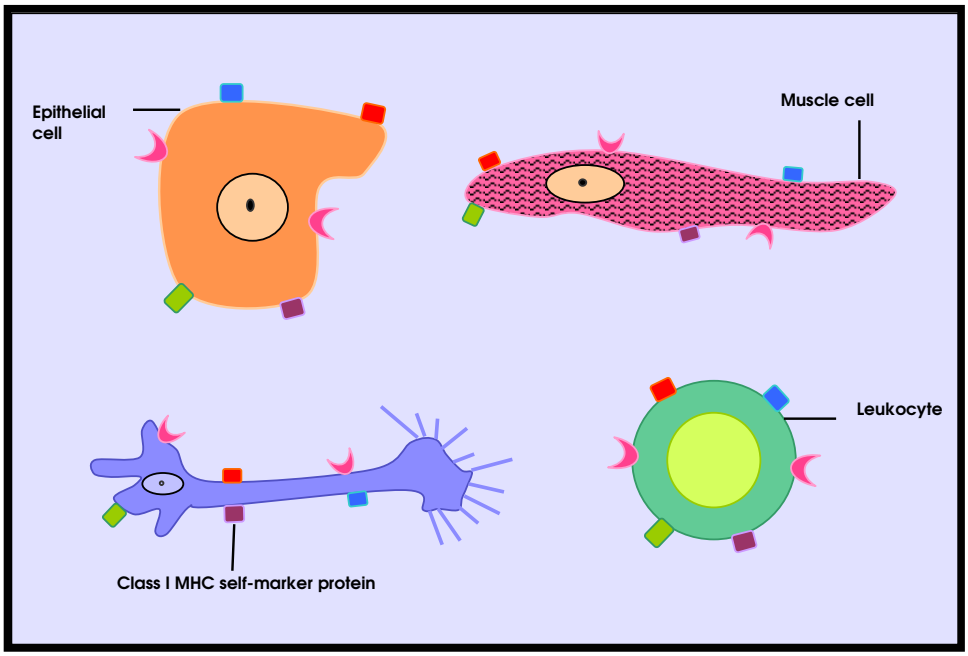

Figure 2.2 Unique markers on host cells ("self" antigens) (Adapted from Schindler *et al*., 2005:3)

When a cell with a set of surface proteins that are not identical to its own enters the body, the body identifies it as foreign. The distinctive markers on the surface of foreign antigens are responsible for triggering an immune response and are called epitopes (Schindler *et al*., 2005:3). Figure 2.3 is an illustration of epitopes on various "non-self" antigens.

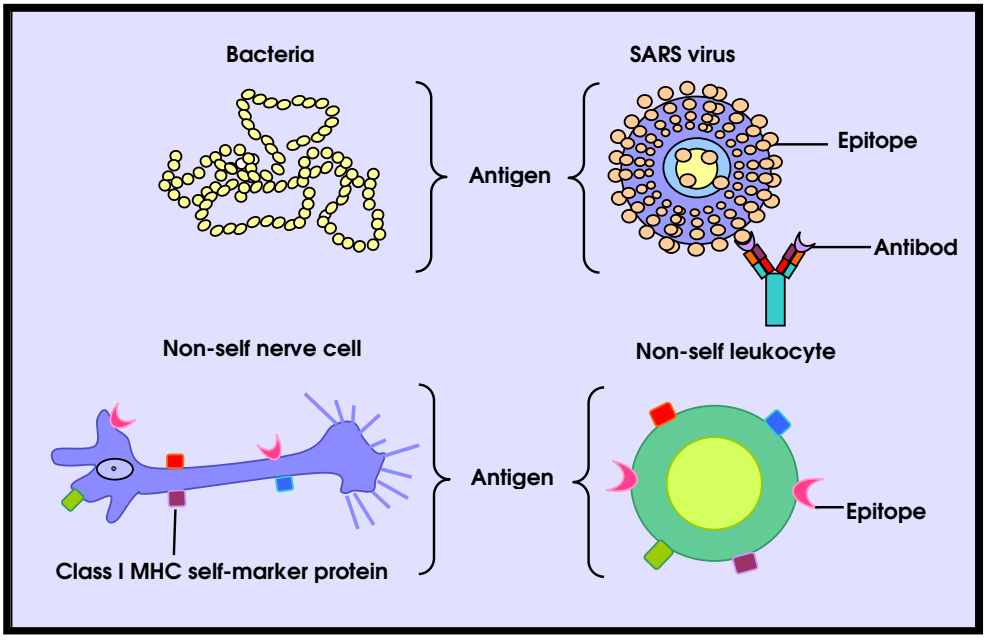

Figure 2.3 Markers on foreign cells ("non-self" antigens) (Adapted from Schindler *et al*., 2005:4)

When a cell carrying antigenic non-self epitopes enter the body, it is attacked by immune cells. Such a cell may be a microorganism, a cell from transplanted tissue, or one of the body's own cells.

The body's own cells get attacked for various reasons, e.g. when host cells are infected by invading microbes, host cells are altered by cancer, or when the body's own proteins act as antigens (Schindler *et al*., 2005:4). When a foreign antigen is recognised by circulating antibodies or cell surface receptors, the immune system is activated. Unless the Ag is phagocytosed quickly and entirely degraded by the cells involved in innate immune response, the acquired immune response is mobilised (Elgert, 2009:7).

The innate and acquired immune responses are the two types of immune responses of the human immune system. Each type of immune response has its own components and unique mechanism of protecting the body against non-self antigens (Chapel, 2006:1). Each response will be discussed briefly.

2.2.1 The innate immune response

Innate immunity is "natural" immunity. People are born with innate immunity and pass it on from generation to generation (Bugl, 2001). The innate immune response is the first line of defence against an antigenic assault and is non-specific (Pathak & Palan, 2005:2). That means that for innate immunity to be effective, it does not need to be previously exposed to an Ag; it thus consists of all the immune defences that lack immunologic memory. As a result, the innate immune system can respond immediately to an invader, and responses occur to the same extent however many times the infectious agent is encountered (Playfair & Chain, 2005:9). The mechanism of protection used by these defences are thus not unique to a particular antigen; instead it mainly recognises Ag molecules that are broadly distributed, rather than specific to one organism or cell (Pathak & Palan, 2005:3).

When the first barrier to infection – an intact skin or mucosa – is broken, bacterial destruction is accomplished by certain biochemical and cellular components (Elgert, 2009:61).

All immune cells originate from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid parent cell and a lymphoid parent cell. From the two parent cells, myeloid cells and lymphoid cells originate respectively.

This constitutes the cellular components of the innate and adaptive immune systems (Mayer, 2009a). Figure 2.4 illustrates the origin of immune cells from a pluripotent stem cell.

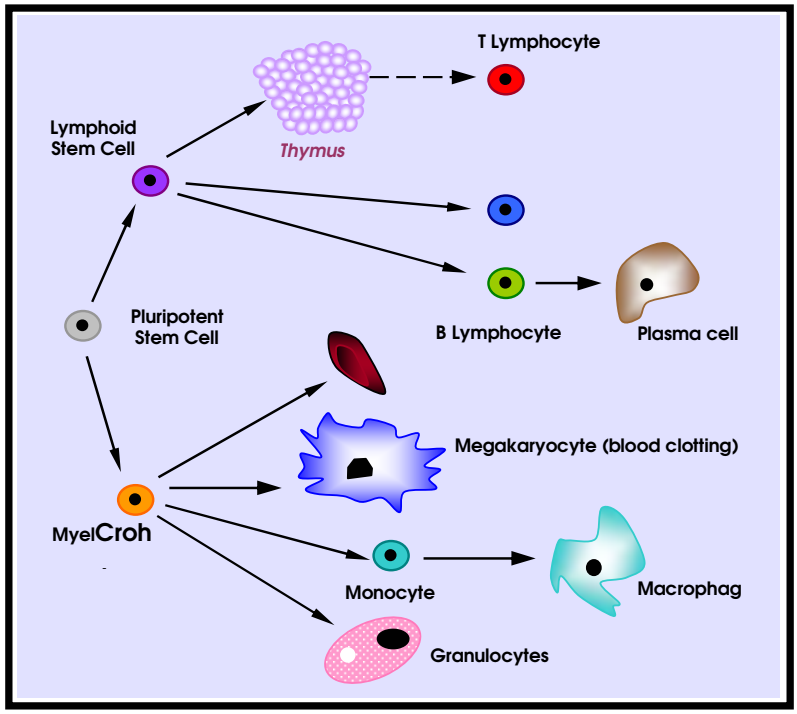

Figure 2.4 Origin of cells of the immune system (Adapted from Grimes and Hallick, 2004)

Elgert (2009:61) lists the components of the innate immune system as below:

- Polymorph nuclear leukocytes.
- Phagocytic cells.
- Ag-presenting cells.
- Natural killer (NK) cells.

Because of the large number of cells and the far larger number of chemical messengers that participate in immune defences, a miniglossary defining the cells and messengers relevant to this study is given in Table 2.1 (innate immune system) and Table 2.2 (adaptive immune system). Cells with less relevance are only briefly described.

Table 2.1 Cells of the innate immune system (Delves & Roitt, 2000:41; Virella, 2007:3; Windmaier *et al*., 2004:697)

Name	*Description*	*Function*
Leukocytes	Collective name for the various types of white blood cells (WBCs). Leukocytes are the most numerous of the immune system cells.	• Phagocytosis. • Release chemicals involved in inflammation.
Polymorpho-nuclear leukocytes	Also called granulocytes because their cytoplasm contains granules.	• Certain polymorphonuclear leukocytes (eosinophils, basophils, mast cells) release inflammatory mediators.
Neutrophils		• Ingest and destroy antigens (Ags) together with other phagocytic cells (monocytes, macrophages and dendritic cells). • Attack by phagocytic cells can be facilitated when Ags are coated with antibodies, which is produced as part of acquired immunity. • Phagocytes also remove body's own dead or dying cells.
Eosinophils	Constitute up to 5% of WBCs. Major source of inflammatory mediators (e.g. prostaglandins, leukotrienes and many cytokines).	• Destroy multicellular parasites. • Participate in immediate hypersensitivity reactions.
Basophils	Constitute less than 5% of WBCs. Share several characteristics with mast cells. Basophiles and mast cells are the source of type 1 hypersensitivity reactions associated with atopic allergy.	• Have functions in blood similar to those of mast cells in tissues.
Mast cells	Occur in different tissues of the body.	• Release histamine and other chemicals involved in inflammation. • By releasing these mediators, mast cells play a key role in generating protective acute inflammatory responses.
Antigen-presenting cells (APCs)	APCs are a heterogenous population of leukocytes that play an important role in innate immunity. Also act as a link to the adaptive immune system by participating in the activation of helper T cells.	• Ag-presenting cells (macrophages, dendritic cells) present fragments of ingested Ags to T cells (which are part of acquired immunity).

Table 2.1 Cells of the innate immune system *(continued)*

	T cell-dependent immune responses require APCs to present antigen fragments combined with MHC molecules. Monocytes, macrophages and dendritic cells constitutively express class II MHC molecules (cell surface molecules encoded by genes in the MHC) and therefore act as professional APCs.	
Monocytes	Monocytes in circulation are precursors to tissue macrophages.	• Have functions in blood similar to those of macrophages in tissues. • Enter tissues and are transformed into macrophages.
Macrophages	Macrophages are activated by interferon γ (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Activated macrophages kill intracellular organisms and secrete interleukin 1 (IL-1) and tumor necrosis factor α (TNF- α) which facilitate leukocyte influx and destruction of pathogens. Macrophages possess receptors for carbohydrates that are not found on the cells of vertebrates and can therefore discriminate between "foreign" and "self" molecules.	• Phagocytosis. • Extracellular killing via secretion on toxic chemicals. • Process and present antigens to helper T cells. • Secrete cytokines involved in inflammation, activation and differentiation of helper T cells, and systemic responses to infection or injury.
Dendritic cells	Dendritic cells are the key cellular components of innate immunity. They are present in the skin, lymph nodes, and tissues throughout the body.	• They become activated and behave as APCs when pattern-recognition receptors on their surface recognise pathogen-associated molecular patterns on the surface of microorganisms.
Natural killer (NK) cells	As cells of the innate immune response, NK cells lack antigen-specific receptors and immunologic memory. NK cells possess killer-activating and killer-inhibitory receptors. Killer-activating receptors recognise various molecules on the surface of normal cells. Inhibitory-cell receptors recognise MHC I molecules. When the inhibitory-cell receptor doesn't elicit a signal, the receptors order the NK to attack and kill the cell.	• Kill virus-infected cells and some tumor (cancer) cells. • Function as killer cells in anti-body dependent cellular cytotoxicity (ADCC). • NK cells can secrete several cytokines [e.g. IFN-γ, IL-1, tumor-necrosis factor α (TNF- α)]; they are a major source of IFN- γ.
ADCC = antibody dependant cellular cytotoxicity; Ags = antigens; APCs = antigen presenting cells; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; NK = natural killer; TNF = tumor necrosis factor; WBCs = white blood cells		

2.2.2 The adaptive immune response

When the innate immune response is unsuccessful to eliminate pathogens, the adaptive immune response is triggered (Lake *et al*., 2004:932). Unlike innate immunity, a person is not born with adaptive immunity, but acquires it throughout his or her life. Adaptive immunity is therefore also called "acquired" or "specific" immunity. The adaptive immune response has the ability to (1) respond specifically to a wide range of antigens, (2) respond to a formerly encountered antigen and (3) distinguish between self and non-self antigens (Decker, 2000:4). Adaptive immunity requires prior exposure to an Ag. After the initial encounter with a new Ag, it takes some time for immunity to develop, but thereafter responses are quick. This system remembers past exposures to specific Ags, which enables adaptive responses to improve on repeated exposures to a given infection (Beers, 2006:1320). Specificity is thus an essential aspect of the adaptive system (Johnston, 2006:337).

The principal active components of the adaptive immune system are a class of white blood cells called lymphocytes (Playfair & Chain, 2005:11). Lymphocytes constitute 20% to 40% of the body's white blood cells (WBCs) of which 20% to 50% circulate in the peripheral blood and 50% to 80% move in the lymph system (Bugl, 2001). Other components of the adaptive immune system are summarised in Table 2.2 (adapted from Virella, 2007:3-4).

As shown in Table 2.2, lymphocytes include B cells, that mature in the bone marrow, and T cells, that mature in the thymus (Elgert, 2009:12). B and T cells are morphologically indistinguishable (Beers, 2006:1322), but some subsets can be defined by the presence and absence of certain surface molecules (Mayer, 2009a). Ag-specific receptors and molecules called clusters of differentiation (CD) are cell surface markers that are used to distinguish between B cells, T cells and their subpopulations. The main distinguishing markers are summarised in Table 2.3 (adapted from Mayer, 2009a).

Table 2.2 Cells of the adaptive immune system (Virella, 2007:3-4)

Name	***Description***	***Function***
B lymphocytes (B cells)	A type of lymphocyte that originates in the bone marrow.	Initiate Ab-mediated immune responses by binding specific Ags to the B cell's surface receptors. Present Ags to helper T cells.
T lymphocytes (T cells)	A type of lymphocyte that originates in the bone marrow.	"Attack" cells that directly kill their targets *via* secreted chemicals.
Cytotoxic T cells	T cells crucial for the annihilation of intracellular pathogens.	Bind to Ags on plasma membrane of target cells and directly destroy the cells.
Helper T cells	T cells that help a variety of other immune cells.	Secrete cytokines that help to activate B cells, and other immune cells.
Suppressor T cells	T cells that mediate suppression of immune responses.	Helps to control the immune response *via* functional subsets of CD4 T cells.
Dendritic cells	Collective term for several cell groups that are not macrophages.	Exert various macrophage functions
Antibodies	Igs secreted by plasma cells.	Direct attacks against Ags or cells bearing them.
Cytokines	Protein messengers.	Act as a chemical communication network.
Complement	Plasma proteins that kill microbes.	Enhances the effectiveness of antibodies.
Ab = antibody; NK = natural killer; CD = cluster of differentiation; Ag = antigen, Ig = immunoglobulin.		

Table 2.3 Main distinguishing markers of B and T cells (Mayer, 2009a)

Marker	***B cells***	***Cytotoxic T cells (Tc)***	***T helper cells (Th)***
CD3	-	+	+
CD4	-	-	+
CD8	-	+	-
CD19, CD40 and/or CD40	+	-	-
Ag-receptor	B cell receptor (BCR)	T cell receptor (TCR)	TCR

Specificity of the adaptive immune response resides in the antigen receptors present on T cells (TCRs) and B cells (BCRs), respectively. Each lymphocyte recognises a specific Ag *via* these surface receptors (Male, 2003:16,18), and it is this ability of lymphocytes to distinguish one antigen from another that confers specificity upon the immune responses in which they participate (Virella, 2007:2).

When adaptive immunity is obtained from selected T-cell responses it is called cell-mediated immunity, whereas immunity that arises from B-cell responses is known as humoral immunity. Since B cells secrete soluble Ag-specific antibodies, humoral responses also refer to antibody-mediated responses (Sell & Max, 2001:5). "Humoral" denotes communication by way of soluble chemical proteins (antibodies) in the blood (Sell & Max, 2001:5).

This adaptive immune response culminates in the production of antibodies, which are effectors of humoral immunity; and the activation of T lymphocytes, which are the effectors of cell-mediated immunity (Windmaier *et al*., 2004:706). B cells and T cells have unique tasks in protecting the body, but they also work together to destroy invaders (Bugl, 2001).

The process by which T cells and B cells interact with antigens is summarised in Figure 2.5.

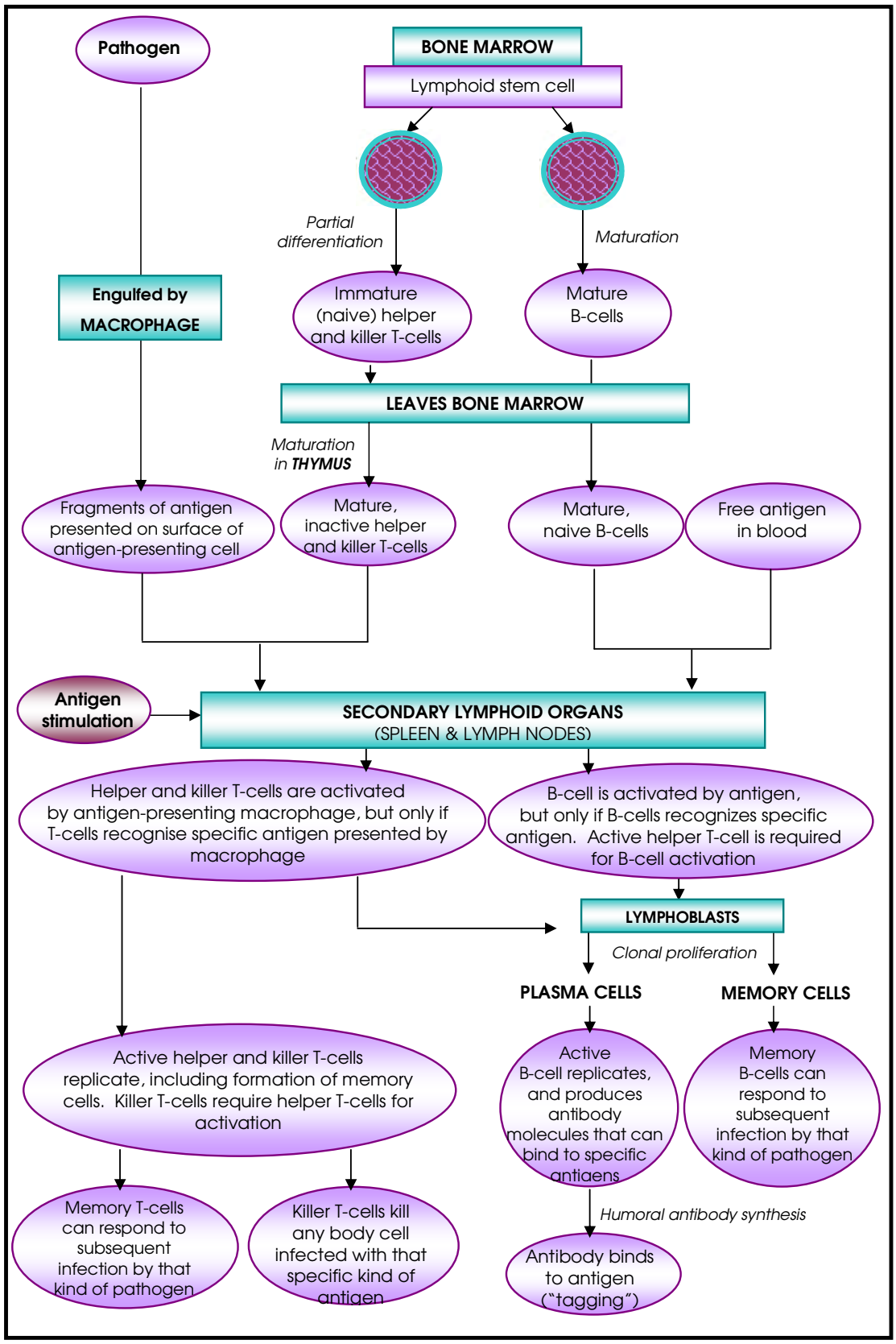

Figure 2.5 Process by which T-cells and B-cells interact with antigens (Adapted from Bugl, 2001)

2.2.2.1 The role of B cells in immune defences

About 5% to 15% of lymphocytes in the blood are B cells. They are also present in the spleen, lymph nodes, and mucosa-associated lymphoid tissues. B cells can present Ag to T cells, but their primary function is to develop into plasma cells, that manufacture and secrete antibodies. B cells are identifiable by membrane expression of immunoglobulins and by B cell-specific CD surface molecules. They also express class II MHC molecules (Eales, 2003:17).

B cells are produced in the stem cells of the bone marrow (Windmaier *et al*., 2004:706). The process starts with a committed stem cell, continues through pro-B and pre-B cell stages, and results in an immature B cell (Bugl, 2001). If an immature B cell interacts with an Ag (self-reactive B lymphocyte), it is clonally deleted. Immature B cells that are not deleted are retained and expanded to develop into mature naive B cells (Pinchuk, 2000:6). B cells leave the bone marrow as mature naive cells and enter secondary lymphoid organs where they may encounter Ags (Keogan *et al*., 2006:15). Figure 2.6 is an illustration of this maturation process.

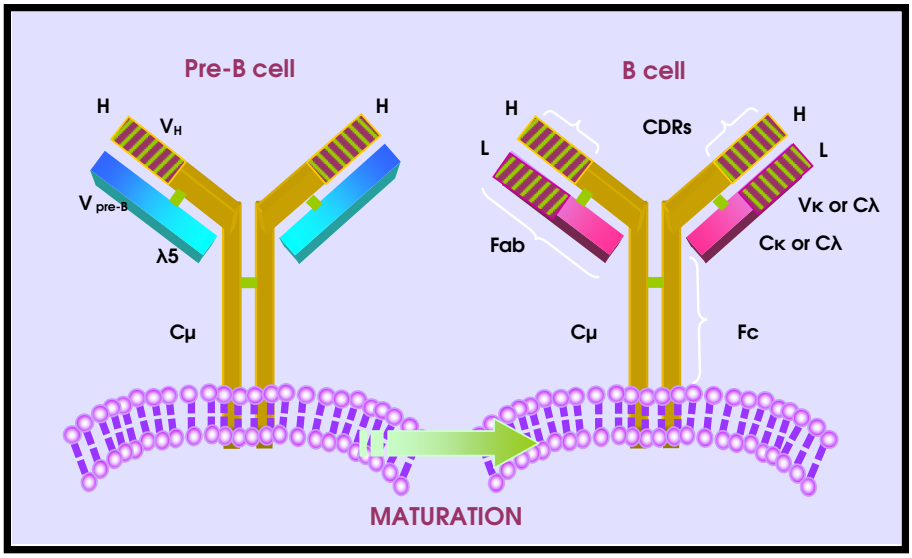

Figure 2.6 Illustration of maturation of B cells in bone marrow (Adapted from Delves & Roitt, 2000:37)

Upon their first encounter with an Ag, mature B cells become lymphoblasts. The B cell internalises and processes the Ag and presents its peptide in the MHC class II to CD4 helper cells, which in turn secrete the interleukins (IL) IL-4 and IL-5. These interleukins stimulate clonal proliferation and differentiation of lymphoblasts into memory B cells and antibody secreting plasma cells (Lake *et al*., 2004:936).

This stage of the response is the primary immune response, and is characterised by a latent period of days before antibodies are produced (Playfair & Chain, 2005:12). Each B cell clone produces an antibody with a single antigen binding specificity (i.e. a monoclonal antibody) (Johnston, 2006:337).

2.2.2.2 The role of T cells in immune defences

T cells, or T lymphocytes, are white blood cells that exert themselves in specific immune responses (Lydyard & Grossi, 2006:11). Like B cells, T cells develop in the bone marrow from stem cells. Unlike B cells, however, T cells leave the bone marrow during fetal and early neonatal life in an immature state and travel to the thymus where they are primed. Mature T cells then move to the secondary lymphoid organs to elicit their immune response (Keogan *et al*., 2006:15).

In an immune response, B cells can recognise antigens directly, whereas T cells need help from other immune cells, called antigen-presenting cells (APCs). APCs are specialised cells that collaborate with T cells in response to the Ag (Delves & Roitt, 2000:37). The main purpose of APCs is to present the Ag to lymphocytes. They can, however, also degrade and often eliminate Ags without the help of T cells (Lydyard & Grossi, 2006:11).

When there are too many antigens, IL-1 is secreted by the APCs and antigen fragments from the invading pathogen(s) are combined with MHC molecules to alert the helper T-cells (Windmaier *et al.*, 2004:710). T cells that encounter IL-1 and fragments of the Ag then learn to recognise the invader's antigen fragments. T cells are then activated and secrete a variety of interleukins that are essential to the success of the immune response (Beers, 2006:1323).

Before T cells can, however, interact with the Ag, they have to undergo two thorough selection processes in the thymus. The first of these two processes is a positive selection process where only those T cells that possess the right set of receptors to recognise the MHC molecules responsible for self-recognition, are extracted. This is followed by a negative selection process whereby T cells that can recognise MHC molecules complexed with Ags are allowed to pass out of the thymus (Burmester *et al*., 2003:12).

During selection, T cells that react to self-Ags presented by self-MHC molecules, are eliminated by apoptosis, while those T cells that are able to recognise non-self Ag-self MHC molecule complexes, survive. It is these cells that then travel from the thymus to secondary lymph tissue and peripheral blood (Male, 2003:115).

In the discussion of immune cells, it is important to first note that all the cells of the human body are coated with various substances. Of these substances, there are well over one hundred and sixty clusters of differentiation (CDs), each of which is a unique chemical molecule that coats the cell surface. T cells in particular have CD2, CD3, CD4, CD28 and CD45R, together with other non-CD molecules (Grimes & Hallick, 2004).

Most mature T cells express either CD4 or CD8 on their surface in addition to having an Ag-binding, immunoglobulin-like surface receptor called the T-cell receptor (TCR). This TCR must connect with Ag-MHC to activate the T cell (Eales, 2003:15). In order for this to happen, T cells must first be sensitised so that they can recognise Ags. T cells are sensitised when macrophages engulf and internally process Ags and then display parts of the Ag, among some of their own proteins, on their surfaces (Grimes & Hallick, 2004).

Other than the TCR-Ag-MHC interaction, there must also be an interaction between co-stimulatory accessory molecules; otherwise the T cell will become anergic or die by apoptosis. Some accessory molecules (e.g. CTLA-4) can, however, inhibit previously activated T cells and thus reduce the immune response (Lydyard & Grossi, 2006:11).

According to Grimes and Hallick (2004), the immune response must at all times be intricately regulated to prevent overwhelming damage to the host. Regulatory, cytotoxic and helper T cells are defined as the three main types of T cells that help to regulate immune responses (Elgert, 2009:36).

Regulatory (suppressor) T cells mediate suppression of immune responses. Regulatory T cells help control the immune response *via* functional subsets of CD4 T cells that either secrete cytokines with immunosuppressive properties, such as IL-10 and transforming growth factor-β (TGF-β), or suppress the immune response by poorly defined mechanisms that require cell-to-cell contact. Regulatory T cells furthermore help prevent autoimmune responses and most likely help to resolve enduring responses to non-self Ags (Virella, 2007:3).

Cytotoxic T (T_C) cells are crucial for the annihilation of intracellular pathogens; viruses in particular. Although T_C cells may be CD4, they are typically CD8. T_C cells are role players in organ transplant rejection (Elgert, 2009:36).

As their name elucidates, helper T (T_H) cells are cells that help a variety of other immune cells. They help B cells recognise and produce antibodies against foreign Ags, they aid killer T cells in becoming active, and they stimulate macrophages to engulf and phagocytise Ags.

In contrast to T_C cells, T_H cells are usually CD4, even though they may occasionally be CD8. All T_H cells differentiate from T_H0 cells into T_H1, T_H2 or T_H17 cells. Each type of T_H cell secretes several cytokines, and different T_H-cell functional phenotypes are identified through different patterns of cytokine production (Elgert, 2009:36).

Furthermore, Burmester *et al*. (2003:20) state that there is clinical relevance in distinguishing between the different T_H cells. A T_H1 response for example, is characteristic of certain autoimmune disorders, such as type 1 diabetes and multiple sclerosis. A T_H2 response on the other hand, promotes immunoglobulin E (IgE) production and development of allergic disorders. T_H2 cells also aid B cells in producing autoantibodies in some autoimmune disorders (e.g. Graves' disease and myasthenia gravis). T_H17 cells may also be a contributing factor in a number of autoimmune disorders, by means of their role in inflammation.

Apart from the three main types of T cells, there are also Natural Killer (NK) T cells. NK T cells are a distinct subset of T cells, which when activated, secrete interleukins and interferons and may help regulate immune responses (Keogan *et al*., 2006:20).

Now that both the adaptive and innate immune systems have been discussed, it is clear that innate and acquired immunity not only work together, but also affect each other; either directly or through substances that attract or trigger other immune cells. These substances include cytokines, antibodies, and complement proteins (Chapel, 2006:10,11).

2.2.3 Antibodies

2.2.3.1 Definition

Antibodies (Abs), also known as immunoglobulins (or Igs) are glycoprotein molecules that are produced by B cells and interact with a specific Ag (Pinchuk, 2000:3). Igs are produced by plasma cells in response to an immunogen and make up the gamma globulin part of the blood proteins (Mayer, 2009c).

2.2.3.2 Antibody structure

Mayer (2009c) states that even though different Abs can vary structurally, they are all built from the same basic unit. Each immunoglobulin molecule is composed of four interlinked polypeptide chains joined by disulfide bonds to produce a Y configuration (Figure 2.7).

The two long chains are called heavy chains, and to two short ones, light chains. The lower half of the two heavy chains, or the "stem", is called the Fc portion (Johnston, 2006:337). The Fc region is crystallisable and determines effector functions, in other words, to which end immune cells can attach. The upper part or Fab (antigen binding) portion of each heavy chain and its associated light chain form an antigen binding site, which are the amino acid sequences that bind specific proteins (epitopes) on the antigen (George, 2000:3).

The heavy and light chains of Abs are divided into a variable (V) region and a constant (C) region. The Fc portions and an extended region of the heavy chains are the same for all immunoglobulins of a particular class. A small portion of the light chains are also the same for a given Ig class. Collectively, these portions of the heavy and light chains are called "constant ends (C)" (Hage, 2005:822). In contrast, the upper part of the light and heavy chains of each Ig contains a variable amino acid sequence (V), which represents the single antigen binding site. The links between the chains represent disulfide bonds (George, 2000:3). Figure 2.7 illustrates the structure of an antibody.

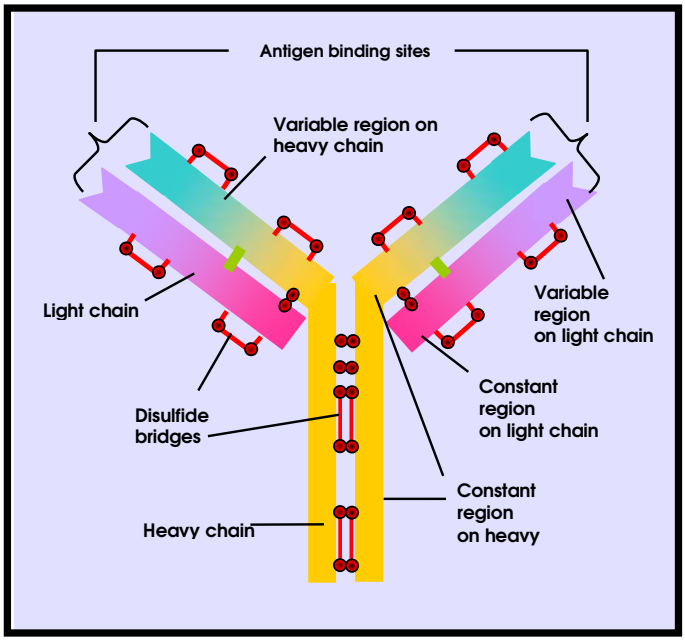

Figure 2.7 Immunoglobulin structure (Adapted from Farabee, 2001)

2.2.3.3 General functions of antibodies

Antigen binding is considered to be the primary function of Abs as this function results in protection of the host (Chapel, 2006:26). The Fab portion of each Ab actually binds specifically to the epitopes of one or a few closely related Ags. Thus, Abs recognise the epitope and not the entire Ag (Mayer, 2009c). The binding of an Ab to an Ag often has no direct biological effect - the significant biological effects are rather a consequence of secondary effector functions of Abs which are mediated by immunoglobulins (Smeltzer *et al*., 2009:1607). This includes the inactivation of antigens *via* complement fixation, neutralisation, agglutination, precipitation and other more peculiar methods of inactivation (Chapel, 2006:26).

2.2.3.4 Antibody classes

There are five major classes of Abs (or immunoglobulins). The classes are determined by the amino acid sequences in the heavy chains and a portion of the light chains and are designated by the letters A, D, E, G and M following the symbol Ig for immunoglobulin; thus IgA etc. (Smeltzer *et al*., 2009:1607). These constituents of gamma globulin are responsible for, amongst others, autoimmune responses, such as allergies and diseases like arthritis, multiple sclerosis, and systemic erythematosus (Burmester *et al*., 2003:28). Table 2.4 (Mayer, 2009c) summarises the major aspects of each antibody class.

Table 2.4 Properties and clinical implications of Ig classes (Mayer, 2009c)

Ig class	*Distinguishing properties*	*Clinical implications*
IgG	Most versatile Ig – can carry out all functions of Ig molecules Major serum Ig – 76% of total serum Ig is IgG Only class of Ig that crosses the placenta	Increases in RA
IgM	Third most common serum Ig (8%) First Ig to be made by the fetus First Ig made by a virgin B cell when stimulated by an Ag	Increases in diseases like RA and lupus erythematosus
IgA	Second most common serum Ig (15%) Major Ig in secretions – tears, saliva, colostrum and mucus	Increases in autoimmune disorders like RA and lupus
IgD	Found in low levels in the serum (1%)	Increases in chronic infections
IgE	Least common serum Ig (0.002%) Involved in allergic reactions	Increases in allergic reactions

2.2.4 Cytokines

2.2.4.1 Overview

Kaufmann and Kabelitz (2002:15) describe cytokines as an assorted group of soluble polypeptides that operate as mediators between cells. Cytokines are secreted by immune- and other cells when the cells interact with a particular Ag, endotoxin, or another cytokine (Cavaillon, 2007:139).

Generally the term cytokine is used to describe a great collection of proteins, but additional terms exist to describe particular kinds of cytokines. Kinds of cytokines include

- monokines, cytokines produced by mononuclear phagocytic cells;
- lymphokines, cytokines produced by activated lymphocytes, especially T_H cells; and
- interleukins, cytokines that act as mediators between leukocytes (Mayer, 2009b).

Cytokines are not normally stored as preformed proteins, but rather produced as they are required in immune responses. According to Cavaillon (2007:139), the primary role of cytokines is to aid communication between different cells of the immune system. Cytokines are thus chemical messengers that attach to specific receptors on target cells with high affinity, and these cells then act in response by altering their function (secretion, proliferation, induction, inhibition etc.) in accordance with the cytokine's message.

Kuchroo and Nicholson (2002:389) add that cytokines are not only important in aiding cellular communication, but also play an important role in the induction and regulation of autoimmune diseases. Mayer (2009b) agrees with Kuchroo and Nicholson's statement, and furthermore explains that it is exactly for this reason that cytokines are currently being clinically used as biological response modifiers for the treatment of various disorders.

2.2.4.2 Categories of cytokines

As stated by Cavaillon (2007:139), the categorisation of cytokines is conditional on the fact that they are produced by and can produce several different cells. Nonetheless, they can be grouped into categories based on their functions or their source.

Male (2003:21), categorises cytokines into six main classes, namely

- Interferons (INFs): INF-alpha, INF-beta, INF-gamma;
- Tumor necrosis factor (TNF): TNF-alpha, lymphotoxin-alpha, lymphotoxin-beta;
- Interleukins (ILs);
- Chemokines;
- Transforming growth factors (TGFs); and
- Hematopoietic colony-stimulating factors (CSFs).

Mayer (2009b) further categorises cytokines as mediators of natural immunity (TNF-α, IL-1, IL-10, IL-12, type I interferons like IFN-α, IFN-β and IFN-γ; and chemokines that all play an important role in the innate immune system), and mediators of adaptive immunity (IL-2, IL-4, IL-5, TGF-β, IL-10 and IFN-γ that are important in the adaptive immune system).

As there is such a wide array of cytokines present in the body, only those with clinical significance applicable to this study will be discussed in short. Table 2.5 (adapted from Chapel, 2006:12-14**;** Mayer, 2009b) is a short review of the most relevant cytokines.

Table 2.5 Selected cytokines (Chapel, 2006:12-14; Mayer, 2009b)

Category	*Cytokine*	*Major sources*	*Main effects*
Interleukins	IL-1a IL-1b	B cells, dendritic cells, endothelium, macrophages, monocytes, NK cells	Co stimulates T-cell activation by enhancing production of cytokines (e.g. IL-2 and its receptor) Enhances B-cell proliferation and maturation Enhances NK-cell cytotoxicity Induces IL-1, IL-6, IL-8, TNF, GM-CSF, and prostaglandin E_2 production by macrophages Is proinflammatory by inducing chemokines, ICAM-1, and VCAM-1 on endothelium
	IL-2	T_H1 cells	Induces proliferation of activate T and B cells Enhances NK-cell cytotoxicity and killing of tumor cells and bacteria by monocytes and macrophages
	IL-6	Dendritic cells, fibroblasts, T_H2 cells, monocytes, macrophages	Induces differentiation of myeloid stem cells and B cells into plasma cells
Interferons	INF-a	Leukocytes	Inhibits viral replication Increases class I MHC expression
	INF-b	Fibroblasts	Inhibits viral replication Increases class I MHC expression
Tumor necrosis factors	TNF-a	B cells, dendritic cells, macrophages, mast cells, monocytes, NK cells, T_H cells	Important mediator of acute inflammation Is cytotoxic to tumor cells Induces secretion of several cytokines (e.g. IL-1) Activates macrophages

GM-CSF = granulocyte-macrophage colony stimulating factor; VCAM-1 = vascular cell adhesion molecule; ICAM-1 = intercellular adhesion molecule; IL = interleukin; INF = interferon; NK = natural killer; TNF = tumor necrosis factor.

2.3 Abnormal immune responses

According to Dean *et al*. (2001:1439), the normally functioning immune response can successfully neutralise toxins, inactivate viruses, destroy transformed cells, and eliminate pathogens, but inappropriate immune responses can lead to certain abnormalities within the body's immune system, including reactivity against self Ags.

Lake *et al*. (2004:936) distinguishes three major types of abnormal immune responses as hypersensitivity, immunodeficiency and autoimmunity. As the focus of this dissertation falls mainly on autoimmune diseases, only autoimmunity will be discussed in detail, whereas only the definitions of hypersensitivity and immunodeficiency will be stated.

2.3.1 Hypersensitivity

Hypersensitivity (allergic reaction) is an excessive immune response to often harmless foreign antigens that damage normal tissues (Levinson, 2006:453).

2.3.2 Immunodeficiency

Immunodeficiency is a condition where the body cannot generate appropriate immune responses against invading microorganisms (Levinson, 2006:471).

2.3.3 Autoimmunity

2.3.3.1 Definition

Autoimmunity is defined as "*the breakdown of mechanisms responsible for self-tolerance and the induction of an immune response against components of the self*" (Ghaffar & Nagarkatti, 2009).

Normally, the body is in a state of immune tolerance toward its own cells. Unfortunately, there are situations in which this tolerance breaks down and the body launches antibody- or killer cell-mediated attacks against its own cells and tissues (Notarangelo *et al*., 2006:322). Ghaffar and Nagarkatti (2009) explains that such an immune response may not always be damaging, however, it is well recognised in several diseases that products of the immune system cause severe damage to the self. When the body mounts an immune response against itself as a result of failure to distinguish self tissues and cells from foreign (non-self) antigens, autoimmune disease arises (Doan *et al*., 2005:10).

2.3.3.2 General classification

Generally, the classification of autoimmune diseases is done on the basis of the organ or tissue involved. These diseases may be organ-specific – in which the immune response is directed against antigen(s) associated with the target organ being damaged – or non-organ-specific (also known as systemic) – in which the antibody is directed against an antigen or many antigens not associated with the target organ and the disease is seen throughout the body (Ghaffar & Nagarkatti, 2009).

2.3.3.3 Etiology of autoimmune diseases

Autoimmune disease is due to an inappropriate immune attack triggered by the body's own proteins acting as antigens. The immune attack, mediated by auto-antibodies and self-reactive cells, is directed specifically against the body's cells that contain these proteins (Friedberg & Johari, 2009:956).

Eales (2003:170) states that although the exact etiology of this immune attack is not known, various theories have been offered. These include sequestered antigen, escape of auto-reactive clones, loss of regulatory T cells, cross-reactive antigens including exogenous antigens (pathogens) and altered self antigens (chemical and viral infections). It is, however, evident that both antibodies and effector T cells and their products can be involved in the damage in autoimmune diseases (Doan *et al*., 2005:157). Some possible causes for the body's failure to recognise its own cells are discussed in Table 2.6 (Windmaier *et al*., 2004:728).

Table 2.6 Possible causes of autoimmune attacks (Windmaier *et al*., 2004:728)

Cause	*Explanation*
Thymus	• There may be failure of clonal deletion in the thymus or of clonal inactivation in the periphery. • This is particularly true for "sequestered antigens", such as certain proteins that are unavailable to the immune system during critical early-life periods.
Environmental factors	• Normal body proteins may be altered by combination with drugs or environmental chemicals. • This leads to an attack on the cells bearing the now-"foreign" protein.
Viruses	• In immune attacks on virus-infected bodily cells, so many cells may be destroyed that disease results.
Genes	• Genetic mutations in the body's cells may yield proteins that serve as antigens.
Microbes with similar structure to "self" antigens	• The body may encounter microbes whose antigens are so close in structure to certain of the body's own proteins that the antibodies or cytotoxic T cells produced against these microbial antigens also attack cells bearing the self proteins.
Other diseases	• Proteins normally never encountered by lymphocytes may become exposed as a result of some other disease.

2.4 Biologics: An Overview

2.4.1 Introduction

Rapid growth in the development of new tools and advances in molecular immunology has led to a new class of medicines called biologics. Recent improvements in the understanding of cellular and molecular pathogenesis of immune diseases, as well as advances in molecular technology have contributed to the development of these medicines, which have been specifically designed to disrupt specific pathogenic processes (Liossis & Tsokos, 2005).

Biologics are medicines comprising various compound classes. Traditionally blood products as well as human and animal cells have been classified as biologics. Today, biologics range from traditional biologics like blood and blood components, fractionated blood products, and antitoxins (Walsh, 2003:2) to modern biologics such as monoclonal antibodies, cytokines (e.g. interferon, interleukin), tissue growth factors, vaccines directed against non-infectious disease targets, and gene transfer products (FDA, 2008:1).

Modern biologics are biotechnology-derived pharmaceuticals, e.g. recombinant therapeutic proteins like monoclonal antibodies, cytokines and growth factors (Tang *et al*., 2004:2184). Modern biologics are mostly used for diagnosis, prevention and treatment of serious and chronic diseases, and are therefore generally termed “therapeutic biologics” (Baumann, 2008:16).

The following section is an overview of biologics and includes concise discussions on the history of biological medicine, the composition and development of biological products and how these products compare to traditional small molecule medicines.

2.4.2 A brief history of biologics

According to Krouse (2008), the first recorded research in biologics began in the 1770s, when Dr. Edward Jenner exposed a test subject to the cowpox virus during his research on the use of viruses to prevent against related diseases. Dr. Jenner monitored an eight-year-old boy after he had been exposed to the virus and allowed his immune system to develop

antibodies against the contaminant. When Jenner then exposed the boy to smallpox and he did not contract the disease from his exposure to the virus, Jenner discovered the first use of a biological treatment in the form of a vaccine (Riedel, 2005:24).

The late 1800s was one of the most exhilarating times for researchers working in biologic research areas around the world (Baker & Katz, 2004:348). In Germany, Robert Koch was investigating and isolating the bacterial organisms responsible for anthrax, rabies, tuberculosis and cholera (Ligon, 2002:289). Louis Pasteur was studying the microorganisms responsible for fermentation and spoilage in France, and developed the first laboratory vaccine against chicken cholera. In America two bacteriologists named Theobald Smith and Edmund Salmon introduced the concept of heat-killed vaccines and used it to prepare a vaccine against hog cholera (Lombard *et al*., 2007:32,43).

The rapidly increasing science of immunology quickly led to the development of new vaccines and antitoxins that promised to prevent and cure some of the most dangerous and feared epidemic diseases distressing mankind (Baker & Katz, 2004:348). These advances in biotherapeutics proved that genetically altered bacterial cells could produce the necessary proteins for biological treatments (Krouse, 2008).

Although concern had been voiced in medical and other accepted literature about the need for regulation, standardisation, and quality control of these new biological products, nothing but talk lay on the table at the turn of the 19th century (White Junod, 2002).

However, when a five-year-old girl died from tetanus in the city hospital in St. Louis in 1901, this swiftly changed. The girl was given a diphtheria anti-toxin and died nine days later. Health officials investigating the case found that some of the anti-toxin being used in the hospital had been contaminated when the horse named Jim, from which the antitoxin had been taken, contracted tetanus (Liu & Davis, 2002:1017). When nine children in New Jersey died from contaminated smallpox vaccine soon after this, the stage was set for the implementation of scrupulous standards for the up-and-coming biological products industry (Milstien, 2004:174).

The Biologics Control Act of 1902 was signed by Theodore Roosevelt on 1 July 1902 to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans (Sanbar, 2004:171). Later, biological products including their manufacturing establishments were licensed under the 1944 Public Health Services Act. The Biologics Control Act and the Public Health Services Act, however, primarily applied to the USA (Labson *et al*., 2008:105). The National Institutes of Health in the US held the

responsibility for biologics in 1948, but in 1972, responsibility for biologics control was transferred to the United States Food and Drug Administration (FDA). (Labson *et al*., 2008:105; White Junod, 2002).

Starting in the 1970s, development of recombinant DNA, large-scale culture technologies and advances in synthetic DNA and protein chemistry have introduced a wide range of new biologics. The first such recombinant therapeutic protein was insulin, and it was approved for general medical use about 20 years ago. By 2003, there were around 140 recombinant proteins with an estimated global market of $30 billion (Baumann, 2006:16).

Recently, the world of biologics has produced not only numerous vaccines but also novel therapeutics to directly combat medical disorders, and seems to be the fastest growing sector of the medical industry at present (Huges & Hann, 2007:60). Since the incorporation of Genentech as the first modern biologics company in 1976 in San Francisco, the proportionately small scope of biological products has expanded greatly. Today, biologics' product range includes treatments for such widespread diseases such as hepatitis C, arthritis, and breast cancer (Krouse, 2008).

The field of biotechnology is obviously on the rise and improving rapidly, and it promises the development of biological medicines with the potential to change the course of modern medicine and its future significantly (Huges & Hann, 2007:59).

2.4.3 Composition and development

Evolving biologics can be defined as products that consist of manipulated, cultured, or expanded human cells, vaccines directed against non-infectious disease targets, and gene-transfer products (Huges & Hann, 2007:59).

Biologics are traditionally derived from living material such as human and animal cells, as well as micro-organisms. Biologics tend to be produced as diverse mixtures of molecules that vary only slightly from one another, which cause them to have very complex and very unique compositions (Genentech, 2009).

Seeing that there is a considerable difference in the manufacturing of individual biological products, the manufacturing agency monitors the production from the early stages to make sure that the final product turns out as expected. Any change in the manufacturing process,

equipment or facilities could alter the biological product itself and therefore further clinical studies are often needed to confirm the product's safety, identity, purity and potency (Keutzer, 2008:422).

Throughout the manufacturing process, purification, formulation, storage and administration of biological products, high levels of solubility, as well as retention of activity, are required (Baumann, 2006:16).

Clinical development of biologics has to be performed, similarly to small molecules, based on appropriate balancing of risks and benefits. The pre-clinical development programme supports the safety of the proposed clinical studies. However, standard pre-clinical testing as used for small molecules is not always appropriate for biologics, as they are often highly species-specific in action and immunogenic in test animal species (Whitmore, 2003:45). The supply of adequate numbers of new biologics in pre-clinical and clinical development is a major concern, with manufacturing costs easily reaching hundredfold that of small molecules. The fact that the pre-clinical development programme has to be planned and performed with the final material is a huge and costly effort (Whitmore, 2003:45).

2.4.4 Biologics *versus* traditional small molecule drugs

Biologics' composition contributes to them being complex mixtures with intricate structures that cannot easily be identified and characterised. Conventional drugs, on the other hand, are chemically synthesised and consist of pure chemical substances.

Chemically synthesised medication preparations have well-defined structures and the active ingredient is clearly identified and can be thoroughly characterised (Keutzer, 2008:421), but the ability to identify the clinically active component(s) of a biological product is often restricted. Therefore, these products are frequently defined and characterised by their manufacturing processes (FDA, 2009a).

Biologics furthermore differ from small molecule drugs in that they tend to be heat sensitive and susceptible to microbial contamination, which requires sterile processes to be applied from initial manufacturing steps (FDA, 2008:2).

Baumann (2006:16) differentiates biologics from conventional drugs by stating that biologics are 2 – 3 orders of magnitude larger than small molecule drugs. Whereas small molecule

drugs are generally composed of 20 to 100 atoms, biologics are composed of anywhere between 200 to 3000 atoms for small biologics like hormones, and 5000 to 50,000 atoms for large biologics like antibodies (Genentech, 2009). To indicate the relative size and complexity of biologics, Genentech compared three drugs – aspirin (small molecule), human growth hormone (hGH), and Herceptin® (an antibody) to three objects. In this comparison, aspirin's complexity was represented by a bicycle, whereas the complexity of hGH and Herceptin® was represented by a car and a business jet accordingly (Genentech, 2009).

The Biologic Finance and Access Council (BFAC) adds another distinction between small molecule drugs and biologics by stating that the majority of biologics are injected or infused, in contrast to traditional prescription drugs that are mostly taken orally (Goff *et al*., 2008:15). Since small molecule drugs can be taken orally, they tend to work within cells in the body. Biologics on the other hand, typically have to be injected because of their size, and therefore interact in the bloodstream or on the surfaces of cells, rather than within cells (Genentech, 2009). Table 2.7 (compiled from Baumann, 2006:16) gives a comparison of the major differences between biologics and traditional small molecule drugs.

Table 2.7 Comparison of small molecule medicines and biologics (Baumann, 2006:16)

Small molecule drugs	***Biologics***
Chemically synthesised	Biotechnologically produced
Single entity, high chemical purity, purity standards well established	Heterogenous mixture, broad specifications which may change during development, difficult to standardise
Oral administration mostly possible	Usually administered parenterally
Often specific toxicity	Mostly receptor mediated toxicity

2.5 Classification and indications of biologics

2.5.1 Introduction

As discussed in chapter one, a single universally precise definition for "biologics" is hard to find. This is also true for the classification of biologics. Neither the World Health Organization's ATC (Anatomical Therapeutic Chemical) classification system, nor the South African "Monthly Index of Medical Specialities" (MIMS) includes a pharmacological group with the title "biologics" that encompass all of the medicines that belong to this group. Biological medicines are labelled as "biologics" based primarily on the nature of their components and the process of manufacturing, but they are usually designated a place in a pharmacological category based on their pharmacological action or indication for use.

The ATC classification, for instance, categorises the majority of the products relevant to this dissertation in category L: *Antineoplastics and immunomodulators* (WHO, 2009), whereas the South African Medicines Formulary (SAMF) categorises the same biologics under the label of "anti-inflammatory and antirheumatic products" (Rossiter, 2010:298). The South African MIMS on the other hand, has included "Biologicals" as group 26 in its pharmacological classification since 2009 (Snyman, 2009:15a), but this group of products mostly included vaccines, blood and blood-derived products, and not the therapeutic biologics relevant to this study. Therefore, despite the inclusion of a group with the designation "biologicals" in the MIMS, the classification of the therapeutic biologics relevant to this study is still greatly miscellaneous.

Etanercept (Enbrel®) for example, is a therapeutic biological medicine item for the treatment of rheumatoid arthritis (RA). It was classified as a musculoskeletal agent (group four) in the 2010 MIMS (Snyman, 2010:82), whereas adalimumab (Humira®), which is also a biological medicine item indicated to treat RA, was classified as an immunological agent (group 24) in the same edition of the MIMS (Snyman, 2010:346). On the other hand, trastuzumab (Herceptin®), a biological medicine item for the treatment of cancer, was classified as a cytostatic (group 23) in 2005 (Snyman, 2005:377), but in the 2010 MIMS, it was classified as a "biological" and designated a place in group 26. The lack of an explicit classification for these drugs thus proves to leave room for interpretation.

However, there is at least one common factor that links the biological medicine with relevance to this research project together: all of the biologics researched in this dissertation were originally manufactured by American pharmaceutical companies, before being exported to South Africa. All the biologics studied in this dissertation are still currently patented only by these American pharmaceutical companies (i.e. Amgen & Wyeth, Abbott laboratories, Genentech etc.).

All biological medicine manufactured in the United States (US) must be approved and licensed for therapeutic use in humans by the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) before it can reach the market (Whitmore, 2003:44). Both the CDER and CBER have regulatory responsibility in the US for therapeutic biological products, including premarket review and oversight (Sanbar, 2004:171). Only once the biological product(s) has been approved and licensed by the FDA may it be exported to, and licensed in other countries – including South Africa. Once a manufacturer wants to export a biological medicine to South Africa, the Medicines Control Council (MCC) takes over regulatory authority.

This same concept of approval and export that applies to the US, also applies to Europe, where the European Medicines Agency have regulatory authority over medicines approval. Europe's biotech companies, however, still have a weak position in the development and marketing of biopharmaceuticals, with only 15% of all biologics having been developed by European biotech companies (Jonsson, 2007:9), none of which is relevant to this study.

Thus, in a matter of speaking, America presently holds the "patent" on the therapeutic biological products researched in this study, and the FDA consequently has the regulatory responsibility for these products regarding both indications, and exports (Schacter, 2006:13).

The FDA's responsibilities regarding biological products include the following (FDA, 2009a):

- Reviewing new biological products and their indications
- Reviewing new indications for already approved products (to introduce biological products to the market for the treatment of common diseases),
- Monitoring the safety of biological products after they have been marketed.

According to Keutzer (2008:421) the FDA's regulatory authority for the approval of biologics resides in the Public Health Service Act (PHS) that allows the FDA not only to approve and

license biological products, but also to immediately suspend licenses when a danger to public health emerges.

Against this background, and the lack of a specific classification system for biologics, the products approved by the FDA as "therapeutic biological products", and the licensed indication for these products will be considered as the framework for the classification of biological products for the purpose of this study.

2.5.2 Classification of biologics

There are four main categories of therapeutic biological products regulated by the CDER (under the Food, Drugs & Cosmetics (FDC) Act and/or the PHS Act, respectively). They include the following:

- **Monoclonal antibodies** for *in vivo* use.
- Most proteins intended for therapeutic use, including **cytokines** (e.g. interferons), **enzymes** and other novel proteins, except for those that are specifically assigned to the Center for Biologics Evaluation and Research (CBER) (e.g. vaccines and blood products).
- **Immunomodulators**,
- **Growth factors**, cytokines, and monoclonal antibodies intended to mobilise, stimulate or otherwise alter the production of hematopoietic cells *in vivo* (FDA, 2009a).

However, the biological products that comprise each category, are unevenly distributed across many different indications, in other words, not all monoclonal antibodies, for example, are used to treat the same disease, or even have the same target receptor. The most reasonable system to classify therapeutic biologics for the purpose of this study is therefore to group them together based on the disease they are indicated for.

Appendix A classifies biologics according to their indications. This list contains all of the medication products that have been approved and licensed as therapeutic biological

products by the FDA's CDER by the end of 2003 – together with their approved indications for use – and is based on the WHO's ATC classification system (FDA, 2009b).

For the purpose of this research project, the researcher identified those therapeutic biological products that are approved and licensed for use in the autoimmune diseases relevant to this project, from the CDER's list (Appendix A). The medicine claims database that has been used in this study, was then consulted and all the biological products relevant to this dissertation were identified (please refer to sections 2.6 and 2.7) and classified according to the ATC classification system, as well as the MIMS classification. This classification is shown in Table 2.8.

Table 2.8 Classification of relevant biologic immunomodulators (Snyman, 2005:92,226,375,379,383; Snyman, 2010:81,200,344,348; WHO, 2009)

Biological medicine	ATC Classification	MIMS Classification	
	December 2009	2005	2010
Adalimumab	Group L: L04AB04 Antineoplastic & Immunomodulating agents - Immunosuppressants	Not included.	Group 24: Immunological 24.1 Immuno-suppressants
Etanercept	Group L: L04AB01 Antineoplastic & Immunomodulating agents - Immunosuppressants	Group 4: Musculo-skeletal agents 4.6 Others	Group 4: Musculo-skeletal agents 4.6 Others
Infliximab	Group L: L04AB02 Antineoplastic & Immunomodulating agents - Immunosuppressants	Group 24: Immunological 24.1 Immuno-suppressants, AND Group 12: Gastro-intestinal tract 12.10 Others	Group 24: Immunological 24.1 Immuno-suppressants, AND Group 12: Gastro-intestinal tract 12.10 Others
Interferon-1a	Group L: L03AB07 Antineoplastic & Immunomodulating agents - Immunostimulants	Group 24: Immunological 24.2 Immuno-stimulants	Group 24: Immunological 24.2 Immuno-stimulants
Interferon-1b	Group L: L03AB08 Antineoplastic & Immunomodulating agents - Immunostimulants	Group 24: Immunological 24.2 Immuno-stimulants	Group 24: Immunological 24.2 Immuno-stimulants
Rituximab	Group L: L01XC02 Antineoplastic & immunomodulating agents – Antineoplastic agents	Group 23: Cytostatics	Group 26: Biologicals

2.5.3 Indications of biologics

Biologics, like other medicines, are used for the treatment, prevention and cure of disease in humans (Baumann, 2006:16; FDA, 2009a).

Biologics, or biological medicine, is typically employed in biological therapy, which the National Cancer Institute (2009) defines as *"treatment that aids the immune system to fight infection and disease"*. Biological therapy thus includes any form of treatment that uses the immune system's natural abilities to fight infection and disease (National Cancer Institute, 2009).

Current forms of biological therapy include monoclonal antibodies, interferons (INFs), interleukins (ILs), and several types of colony stimulating factors (CSF, GM-CSF, G-CSF) known as recombinant cytokines (National Cancer Institute, 2009). Monoclonal antibodies and cytokines represent the largest portion of the continually increasing number of recombinant proteins presently being marketed as therapeutics (Tang *et al*., 2004:2184).

Biological medicine is used in the treatment of a number of different conditions. Mostly, biologics are indicated to treat long-term and/or life-threatening diseases, like cancer, HIV/AIDS, rheumatoid arthritis, multiple sclerosis, anemia, hepatitis C, organ transplants and complications caused by human growth hormone (Cohen *et al.,* 2006:S25). Cura Script Specialty Pharmacy, a company of the American pharmacy benefit manager Express Scripts, agrees that even though the prevalence of the above-mentioned diseases is still quite low when weighed against other chronic diseases like congestive heart failure or diabetes, biological medicines have nonetheless become imperative in the treatment of previously hard to treat chronic illnesses (Fontanez *et al*., 2005:3).

Through the development and improvement of biologics, a wide variety of medical conditions, including illnesses for which no other treatments were previously available, can now be treated, and the future promises to yield many more treatments for formerly untreatable illnesses (FDA, 2008:1).

2.5.4 Prevalence of use of biologics

Goff *et al.* (2008:15) predicted in 2008 that increased utilisation of biologics will propel the growth in future drug spending. They also suggested that the primary reason for increased utilisation of biologics would not be the introduction of new biologics, but rather additional indications for already existing biologics.

Reports by Datamonitor (2007) supported Goff *et al*.'s statement, as it indicated that the biologics with the highest prevalence and greatest potential for future growth were the monoclonal antibodies used in the treatment of chronic diseases and cancer (Datamonitor, 2007).

The two chronic diseases multiple sclerosis and rheumatoid arthritis, were indicated as two of the top diseases – excluding cancer – that were treated with biologics in 2004 (Fontanez *et al*., 2005:37). In their Specialty Pharmacy Management Guide and Trend Report for the same year, Cura Script Specialty Pharmacy calculated the percentage medicine costs spent on biologics per diseases, indicating in which therapy class biologics had the highest utilisation trend (Fontanez *et al*., 2005:37). Miscellaneous central nervous system agents for the treatment of multiple sclerosis, in combination with rheumatic arthritis agents for the treatment of rheumatoid arthritis, contributed to almost half of total overall biological drug trends for Cura Script clients in 2004 (Figure 2.8).

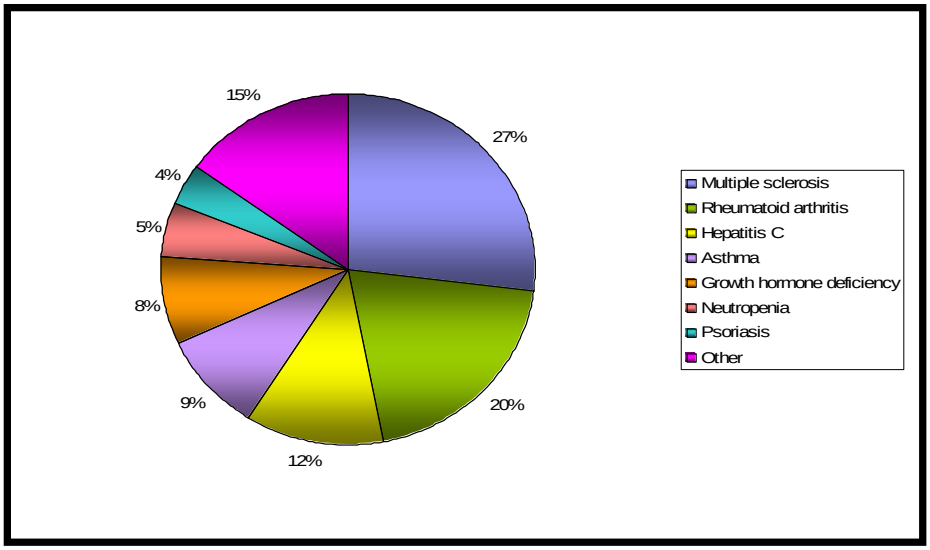

Figure 2.8 Percentage biological medicine spend per disease in 2004 (Compiled form Fontanez *et al*., 2005:37)

In 2007, Lawrence (2007:381) reported on the "biopharmaceutical blockbusters" that were fast making way in the drug industry. This report showed that of the 12 top-selling biologic products in the USA in 2005 and 2006, most were used in oncology (Rituxan®, Herceptin® and Avastin®), either as direct therapy for malignancies or as supportive therapy. The treatment of autoimmune disorders (such as RA, Crohn's disease and psoriasis) was the chief use for most of the other top sellers (Enbrel®, Remicade® and Humira®) (Figure 2.9) (Lawrence 2007:381).

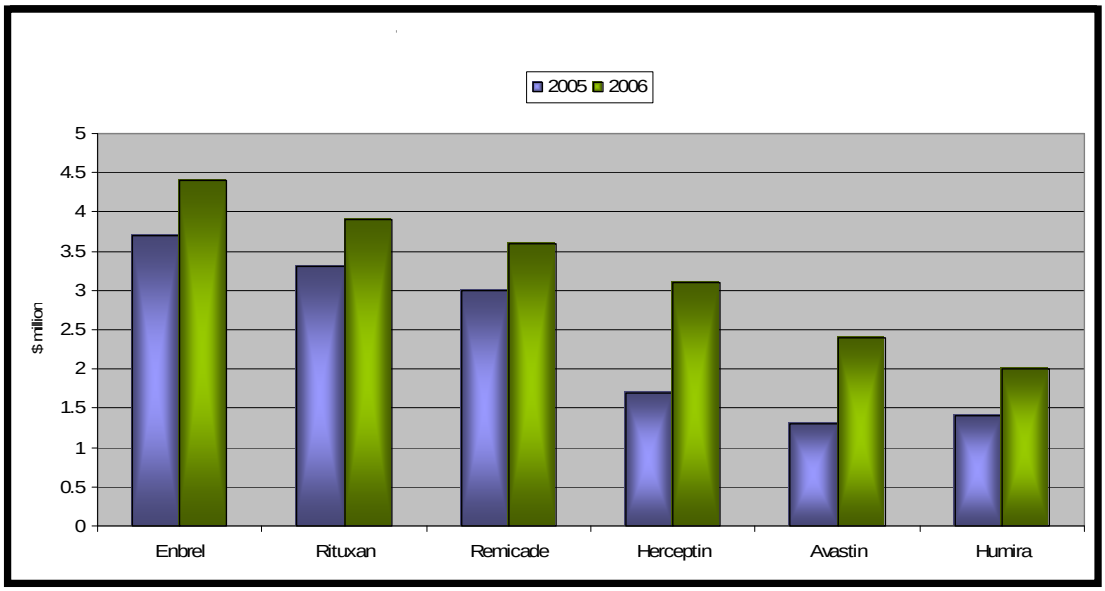

Figure 2.9 Top biological medicines by US sales (Compiled from Lawrence, 2007:381)

According to a drug trend report for the same year by an American PBM, Express Scripts (Meyer *et al.,* 2007:29), inflammatory conditions (including Crohn's disease and rheumatoid arthritis) drove the utilisation trend for specialty therapies in this class to 22.7% from 2006 to 2007. By the end of 2008 the utilisation trend for specialty therapies used to treat inflammatory conditions increased to 27.5%, whereas the utilisation trend for cancer was only 16%. Inflammatory conditions, multiple sclerosis and cancer were the top three specialty classes in America in 2008 and accounted for nearly 64% of specialty spent in 2008 (Figure 2.10) (Cox *et al*., 2009:32).

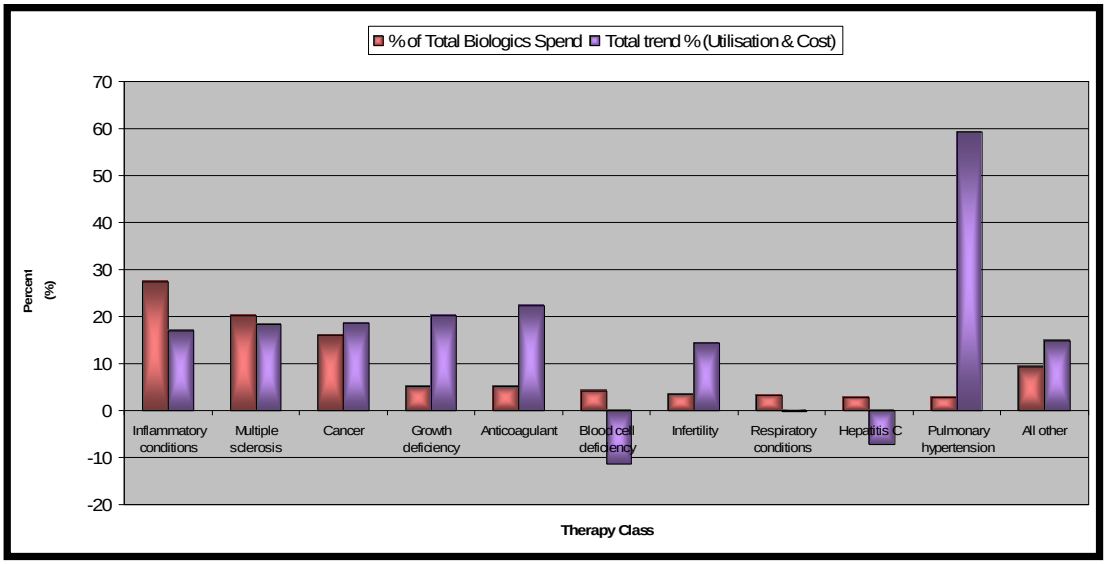

Figure 2.10 Top 10 biological therapy classes ranked according to percent of total biological utilisation and spent (Compiled and adapted from Cox *et al*., 2009:32)

Thus, drug trend reports from both Cura Scripts Pharmacy (2005) and Express Scripts (2008) reflected the same biological drug trends for their respective clients in America, over a four-year period from 2004 to 2008. Also Lawrence's (2007:381) report concurred that when cancer was excluded, inflammatory conditions (like rheumatoid arthritis) and multiple sclerosis had been two of at least the top five diseases being treated with biologics in the USA from 2004 to 2008.

The biologics trend in South Africa corresponded with these statistics. In South Africa, Bester and Badenhorst (2009:14) indicated the top five therapeutic groups according to expenditure for Mediscor® beneficiaries in their 2008 drug trend report. The cytostatics presented as the third highest contributor to medical expenditure in 2008, of which five cytostatic agents featured on the top 50 product list, including the biological breast cancer drug Herceptin® (position 3) and the biological RA and cancer drug MabThera® (position 15), but these medicine items only represented only 1.7% of the total number of medicine items claimed through the PBM during 2008 (Bester & Badenhorst, 2009:14). In this instance, the therapeutic class "cytostatics" not only includes biologics used in the treatment of cancer, but also biologics used to treat several autoimmune diseases. The RA drug Enbrel® was the only other biological medicine item featured on this list (position 42), and represented just 0.3% of the total number of medicine items claimed through the PBM that year (Bester & Badenhorst, 2009:14). The data from one South African Pharmacy Benefit Management (PBM) company thus indicated that biological medicine items only represented about 2% of the total number of medicine items claimed through the PBM in one year.

Even though only one PBM's data were obtained, it can be presumed (from the available literature) that the prevalence of biologics in South Africa is low. Furthermore, both national and international literature indicated that apart from cancer, most other therapeutic biologicals on the market today are being used to treat chronic inflammatory conditions like rheumatoid arthritis, psoriasis, Crohn's disease and also multiple sclerosis. Cohen *et al*. (2006:S25) also state that of the biopharmaceuticals still in late-stage development and pending FDA approval for impending market launches, cancer is certainly the top target disease, followed by infectious diseases and autoimmune disorders like rheumatoid arthritis.

It was against this background that the researcher chose to do further research on the biologics especially used to treat the chronic inflammatory conditions mentioned above. As the selected conditions are all classified as autoimmune disorders and often treated with the same biologics, the overall focus of this study will be on biologics used to treat autoimmune diseases, with special focus on biologics indicated for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease.

2.6 Biologics used in the treatment of autoimmune diseases

As stated by Van Eden *et al*. (2009:1), there are a number of specific challenges in the immunotherapy of autoimmune diseases that cannot be solved by means of conventional approaches. Despite the many unresolved issues surrounding the reasons for autoimmunity, researchers do know that the basic principle of autoimmune diseases involves the production of carrier substances that falsely inform the body of ongoing infection. These substances cause the immune system to launch a strong immune response that repeatedly attacks and destroys the body's own tissues. According to Boehncke and Radeke (2007:1), the key to altering this continuous process of destruction, lays in understanding specific models of destruction.

Fortunately, there has been a remarkable change in the immunotherapy of autoimmune diseases in which biological agents, such as monoclonal antibodies, soluble receptors and molecular mimetics, present the potential to improve or substitute conventional immunosuppressive therapies (Nepom, 2002:812). Biologics were developed with two aims in mind: to specifically jump-start the immune reaction, or to specifically target tumors and kill them (Boehncke & Radeke, 2007:1). According to Nepom (2002:812), the vision for substantially expanding alternatives for the treatment of autoimmune diseases rests on thoughtful design of trials utilising these biologic agents.

During the last 8 to 10 years, clinical efficacy trials have been successfully completed for an increasing selection of new biologics, several of which are promising immunotherapeutic biologics that target distinct pathways in the adaptive immune response (Nepom, 2002:812).

Ordinarily, a single molecule or pathway is targeted when treating an autoimmune disease. This is typically achieved by developing a competitive antagonist of the natural receptor or a soluble imitator of the receptor to meddle with the action of an unwanted protein in order to reduce its amount in the circulation (Van Eden *et al.,* 2009:1). This is a highly focused, traditional strategy that leads to most of the biologics currently in use. However, mounting evidence regarding the diversity of pathogenic elements linked in the underlying autoimmune process suggests that, instead of targeting individual immune elements, novel therapies should rather target actions of immune functions (Van Eden *et al*., 2009:1). Some possible targets and pathways are illustrated in Figure. 2.11.

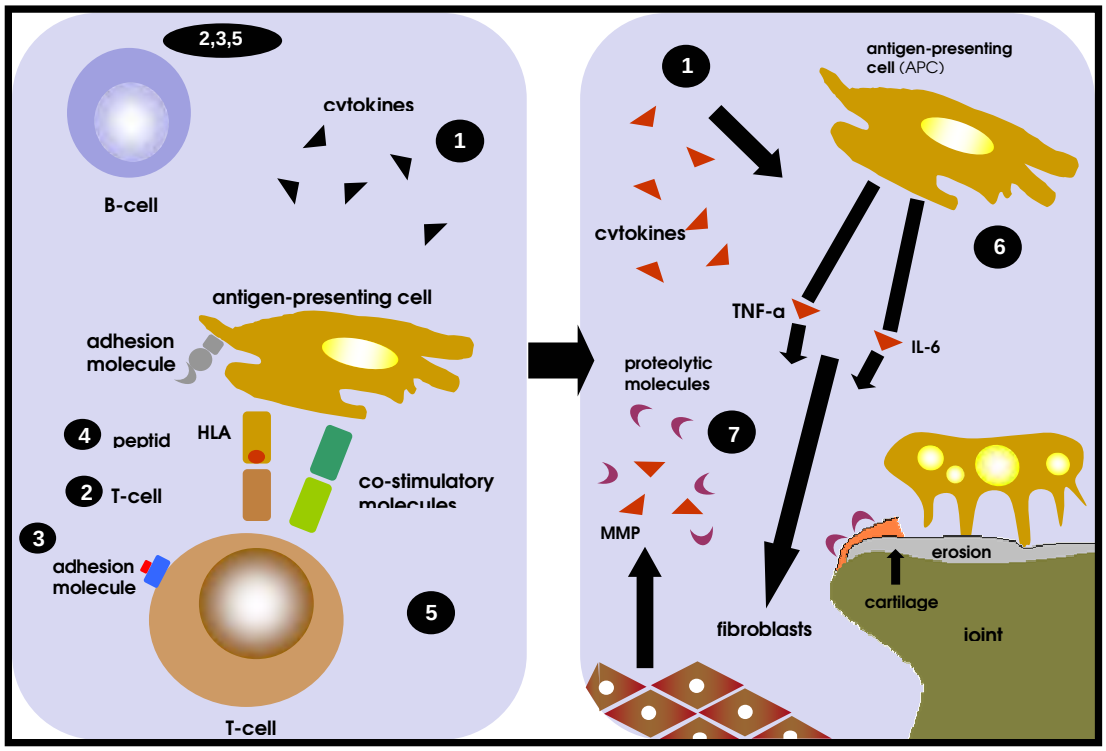

Figure 2.11 Therapeutic targets of biological medicines (Adapted from Van Eden *et al*., 2009:2)

(1) Anticytokine therapies. **(2)** Therapies directed toward the T or B cell receptor. **(3)** Approaches interfering with adhesion and migration of the immune cells. **(4)** Antigen specific tolerisation. **(5)** Therapies interfering with pathways related to the modulation of the intensity and quality of immune responses. **(6)** Therapies interfering with intracellular signaling. **(7)** Inhibitors of the final mediators of damage.

Table 2.9 (compiled from Ballow, 2006:1210-1212; FDA, 2009b; Rossiter, 2010:64,398) contains the names of therapeutic biologics approved by the FDA's CDER to treat autoimmune diseases (FDA, 2009b). The therapeutic target of each biological product will be indicated with a number as assigned in Figure 2.11.

Table 2.9 FDA approved therapeutic biological products indicated for autoimmune conditions* (Ballow, 2006:1210; FDA, 2009b; Rossiter, 2010:64,398)

Active ingredient	*Trade name*	*Target or pathway*	*Autoimmune condition*
Abatacept	Orencia®	(2)	RA
Adalimumab	Humira®	(1)	RA, JRA, PsA, AS, Crohn's disease, Ps
Alefacept	Amevive®	(2)	Plaque psoriases
Anakinra	Kineret®	(1)	RA, Still's disease
Basilliximab	Simulect®	(1)	Acute kidney rejection
Certolizumab pegol	Cimzia®	(1)	Crohn's disease
Daclizumab	Zenapax®	(2)	Acute kidney rejection
Efalizumab	Raptiva®	(5)	Psoriases
Etanercept	Enbrel®	(1)	RA, JRA, PsA, AS, Crohn's disease, Ps
Infliximab	Remicade® Revellex® *(South Africa)*	(1)	RA, Crohn's disease, PsA, AS, UC, Ps
Interferon beta 1-a	Avonex®	(5)	MS
Interferon beta 1-a	Rebif®	(5)	MS
Interferon beta 1-b	Betaseron® Betaferon® *(South Africa)*	(5)	MS
Interferon gamma 1-b	Actimmune®	(5)	Osteoporosis
Muromonab-CD3	Orthoclone OKT3®	(2)	Heart, kidney and liver rejection
Natalizumab	Tysabri®	(5)	MS, Crohn's disease
Rilonacept	Arcalyst®	-	FCAS
Romiplostim	Nplate®	-	Chronic ITP

***Does not include biologic immunotherapeutics used for cancer or other immune disorders, e.g. allergic conditions or immunodeficiency disorders.**

FCAS = Familial cold autoinflammatory syndrome; ITP = idiopathic immune thrombocytopenic purpura; JRA = juvenile rheumatic arthritis; MS = multiple sclerosis; RA = rheumatoid arthritis; Ps = plaque psoriasis; PsA = psoriatic arthritis.

Table 2.10 (Beers, 2006:1329; FDA, 2009b; Rossiter, 2010:64) reduces the scope of Table 2.9 by only containing the names of the biologics used in the four autoimmune diseases selected in section 2.5.4 for further investigation.

Table 2.10 FDA approved biological products used in selected autoimmune diseases (Beers, 2006:1329; FDA, 2009b; Rossiter, 2010:64)

Active ingredient (Trade name)	*Description / Effect*	*Available in SA*	*Available on data**	*Indication(s)*
Alefacept *(Amevive®)*	Dimeric fusion protein consisting of the extracellular CD2-binding portion of human LFA-3 linked to Fc portion of human IgG1	No	No	Psoriasis
Interferon β-1a *(Avonex® / Rebif®)*	Recombinant cytokine with antiproliferative and antiviral properties	Yes	Yes	MS
Etanercept *(Enbrel®)*	Soluble human TNF-α receptor protein	Yes	Yes	RA, PsA, AS, Ps, JRA
Adalimumab *(Humira®)*	Anti-TNF-α monoclonal antibody (humanised)	Yes	Yes	RA, JRA, PsA, AS, Crohn's disease, Ps
Anakinra *(Kineret®)*	Recombinant, nonglycosylated form of human interleukin-1 receptor antagonist (IL-1Ra)	No	No	RA
Interferon β-1b *(Betaseron® / Betaferon®)*	Recombinant cytokine with antiproliferative and antiviral properties	Yes *(Betaferon®)*	Yes *(Betaferon ®)*	MS
Infliximab *(Remicade® / Revellex®)*	Anti-TNF-α monoclonal antibody (Chimeric)	Yes *(Revellex®)*	Yes *(Revellex®)*	RA, Crohn's disease, PsA, AS, UC, Ps
Certolizumab *(Cimzia®)*	Anti-TNF-α monoclonal antibody	No	No	Crohn's disease
Efalizumab *(Raptiva®)***	Monoclonal antibody against CD11 (humanised)	No	No	Psoriasis
Natalizumab *(Tysabri®)*	Anti-α_4-integrin subunit	No	No	MS, Crohn's disease
Abatacept *(Orencia®)*	Selective T-cell co-stimulation modulator fusion protein	No	No	RA
Rituximab *(MabThera®)*	B-cell depleting monoclonal antibody against CD20 (chimeric)	Yes	Yes	RA
Tocilizumab *(Actemra®)*	Humanised monoclonal anti-IL-6 receptor antibody	No	No	RA

***Research data for the purpose of this study**

****Efalizumab (Raptiva®) has been withdrawn from the market. Raptiva® was approved by the FDA in 2003 for moderate to severe plaque psoriasis. The manufacturer of Raptiva®, Genentech, however announced on 8 April 2009 that it began a phased withdrawal of the product from the U.S. market, because of a potential risk of developing progressive multifocal leukoencephalopathy (PML); a rare, serious, progressive neurologic disease. By June 8, 2009, Raptiva® was no longer available in the US, and could therefore not be exported to other countries (including South Africa) after this date (FDA, 2009c).**

MS = multiple sclerosis; RA = rheumatoid arthritis, AS = ankylosing spondylitis, Ps = plaque psoriasis, PsA = psoriatic arthritis, UC = ulcerative cholitis, LFA-3 = leukocyte function antigen-3.

Psoriasis is one of the autoimmune diseases indicated by literature as one of the most prevalent chronic inflammatory conditions treated with biologics, and it was therefore selected as one of the autoimmune diseases chosen for further investigation (refer to section 2.5.4), but since the biologics specifically indicated for psoriasis (Amevive® and Raptiva®) are not available for therapeutic use in South Africa, and thus also not available on the research data (as shown in Table 2.10), the researcher decided not to include psoriases in further research.

The RA biologics Anakinra® and Orencia®, the Crohn's disease biologic Cimzia® and the MS and Crohn's disease biologic Tysabri® are also not available on the research data and was consequently excluded from this study.

2.7 Biologic immunomodulators used in the treatment of rheumatoid arthritis, Crohn's disease and multiple sclerosis

In order to understand the importance of biologic immunomodulators in autoimmune disorders, this section will include brief discussions on each of the selected autoimmune conditions. Each discussion will include a definition of the autoimmune disease being discussed; disease prevalence by age and gender; clinical presentation; criteria for diagnosis; desired outcome and pharmacological therapy, with a distinction between traditional medicine therapy and biological immunotherapy.

2.7.1 Rheumatoid arthritis (RA)

2.7.1.1 Definition

RA is a *"chronic, inflammatory, destructive, and sometimes deforming collagen disease that has an autoimmune component. It is characterised by symmetric inflammation of synovial membranes and increased synovial exudates, leading to thickening of the membranes and swelling of the joints that, if left untreated, results in joint deformity and destruction"* (Myers, 2006:1634).

2.7.1.2 Disease prevalence by age and gender

According to Longmore *et al.* (2007:532), RA affects approximately 1% of the population, with higher disease prevalence among smokers. RA can begin at any age, but peak onset is in the 4th and 5th decade for women, and the 6th to 8th decade for men. Mean age of onset for RA is 45 years. RA is more common in women than in men (ratio of women to men is 3:1) (Hellmann & Imboden, 2008:721).

2.7.1.3 Pathogenesis

The exact cause of RA remains uncertain. It does however appear that when an individual who is genetically predisposed to develop RA is exposed to an exogenous agent, the synovial inflammation of RA is triggered. According to Hellmann and Imboden (2008:721), the major genetic risk factor for RA is believed to be the "shared epitope", a common amino acid sequence, since this epitope is present in up to 90% of RA patients.

Tikly (2009:284) maintains that even though the precise etiology of RA is not evident, it is acknowledged that inflammation is the main biological event in RA: monocytes travel into the joint, which triggers the production of cytokines; this causes the activation of fibroblasts and endothelial cells, which is followed by tissue proliferation. Cytokines, together with cellular processes and fluid generation, cause cartilage and bone erosion. Cytokines also contribute to systemic affects like fatigue, accelerated atherosclerosis, and quicker bone turnover (Longmore *et al*., 2004:533).

Angiogenesis, endothelial cell activation and synovial cell hyperplasia are early pathologic events of RA. These events are caused by T-cells, macrophages and fibroblasts that infiltrate the synovium, and results in cartilage and bone destruction, for which abnormal production of various cytokines, particularly tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6), are to blame (Tikly, 2009:284). Figure 2.12 illustrates the pathways involved in inflammation and destruction in the rheumatoid joint.

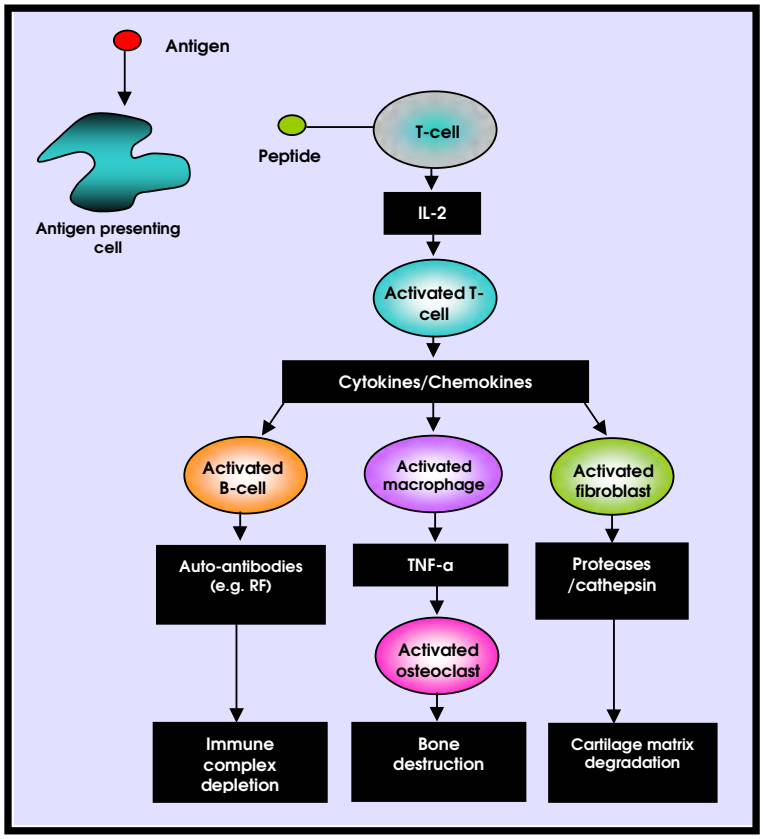

Figure 2.12 Pathways involved in inflammation and destruction in the rheumatoid joint (Adapted from Tikly, 2009:285)

2.7.1.4 Clinical presentation

RA typically presents with symmetrical swollen, painful and stiff small joints of the hands and feet that is generally worse in the morning. Symmetrical swelling of the joints is the earliest sign of RA. The joints typically involved are the metocarpo-pharangeal, proximal interphalangeal and metatarsal joints, as well as the wrists. Swelling usually indicates only inflammation, without joint damage. Joint damage and deformity follows as the disease progresses and presents as ulnar deviation of the fingers and dorsal wrist subluxation. The extensor tendons of the hands may eventually rupture, and larger joints may become involved as the disease progresses. The extent of the joint damage classifies the disease into four stages of severity (Hellmann & Imboden, 2008:721).

According to Myers (2006:1634), RA may also be classified on the basis of a patient's functional capability. According to this method of classification, a patient is in: class I when he or she has no loss of function; class II when the patient suffers minor impairment of functional capability with some pain and immobility; class III when the patient's capacity is limited to a few tasks; and class IV, when the patient is confined to bed or to a wheelchair.

Lee and Kavanaugh (2003:811) state that even though spontaneous remission of RA can occur, it mostly progresses to a chronic state associated with significant functional disability.

2.7.1.5 Diagnostic criteria

According to Hellmann and Imboden (2008:721), there is no single physical sign or laboratory test that is diagnostic of RA; rather, the diagnosis of RA is based on the presence of a constellation of symptoms, signs, serological findings and radiographic abnormalities.

A patient that thus presents with at least four of the following criteria is positively diagnosed with RA: 1) joint stiffness lasting more than an hour in the morning, 2) arthritis of three or more joints, 3) arthritis of hand joints, 4) symmetrical arthritis, 5) rheumatoid nodules, 6) radiographic changes, and 7) positive ventricular extra systole rheumatoid factor*. A positive diagnosis for RA further requires that the first four criteria be present for at least six weeks (Longmore *et al*., 2007:532).

2.7.1.6 Desired outcome

Goff *et al*. (2008:16) proclaim that, now that medical practitioners have a better understanding of the natural history of RA, and more effective treatments for the disease are available, the goal of treatment is to achieve remission of RA at an early stage in order to prevent long-term structural damage and disability. According to Naz and Symmons (2007:871), some 30% to 40% of RA patients experience work disability within five years of onset of the disease. They add that the life expectancy of individuals affected by RA is also reduced by about 10 years, largely due to accelerated cardiovascular disease, infections and respiratory complications.

In accordance with Goff *et al.*'s statement, Tikly (2009:287) appoints the two primary goals of RA treatment as reducing patients' pain and discomfort, and trying to prevent or minimise physical disability associated with the disease progress.

***Rheumatoid factor (RF) is an antiglobulin antibody, typically of the IgM class, directed against self-IgG (Myer, 2006:1634). RFs are often found in the serum of patients with a clinical diagnosis of RA, and is therefore one of the criteria for diagnosis for RA. Although RFs are present in about 70% of RA cases, it is not useful as a screening test for RA in the general population, as it is not specific for RA – RFs are also found in such widely divergent diseases as tuberculosis, parasitic infections, leukemia, and connective tissue disorders. RF is therefore most clinically useful when there is a moderate pretest likelihood of RA (Chaiamnuay & Bridges, 2005:208).**

Table 2.11 (Tikly, 2009:287) summarises the principles of treatment to achieve the desired outcome.

Table 2.11 Principles of medical management of RA (Tikly, 2009:287)

Ensure diagnosis of RA is correct.
Provide joint protection education.
Discourage cigarette smoking.
Early intervention with DMARDs for all patients with persistent synovitis.
Adjunctive treatment with analgesics and NSAIDs for pain management.
Intra-articular steroids for the treatment of one or a few actively inflamed joins.
Oral corticosteroids in low doses (≤ 10mg/day) as "bridging therapy" in combination with DMARDs.
Biologics for DMARD-refractory disease.
RA = rheumatoid arthritis; DMARDs = disease modifying antirheumatic drugs; NSAIDs = non-steroid anti-inflammatory drugs.

There is thus cause for optimism in terms of the long-term outcome of RA, thanks to early aggressive medical treatment. The risk of joint deformities, physical disability and death has greatly been reduced because of the combination of simple clinical tools to measure disease activity, the use of traditional disease modifying antirheumatic drugs (DMARDs) early in the disease and the introduction of targeted biologic agents (Tikly, 2009:284). De Vries-Bouwstra *et al*. (2005:745) are of the opinion that the development of biologic agents has enabled remission as a realistic goal in a greater portion of patients.

2.7.1.7 Pharmacological treatment

According to Lee and Kavanaugh (2003:811), the current therapeutic model for RA embraces a step-up approach that safely combines several classes of medicines that are currently available to treat RA. These classes include the non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclo-oxygenase-2 inhibitors, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), which are the "traditional" or small molecule therapies, and also biological agents (Lee & Kavanaugh, 2003:811).

- *Traditional RA therapies*

In earlier years, RA patients were often treated according to the traditional "therapeutic pyramid" that was established by rheumatologists, which started with non-pharmacological measures and NSAIDs. DMARDs were reserved for patients who exhibited persistent disease progression despite supportive measures. The traditional pyramid has, however, been modified to reflect the introduction of alternative agents. Supportive data containing evidence that RA is in fact an aggressive disease that causes erosive joint damage – even within the first two years of the disease – and the fact that the progressive joint damage as well as related impairments in functional status is connected to the substantial economic costs associated with RA have also been taken into consideration for the revision of the treatment regime (Lee & Kavanaugh, 2003:812). Successful treatment of RA thus requires early aggressive pharmacological intervention. This concept has been incorporated in the more recent treatment regime. The standard "step-up" approach as it is currently known is illustrated in Figure 2.13, which is the current treatment algorithm of RA as published by the Council for Medical Schemes. This treatment protocol of RA shows that RA patients should be treated with "traditional" medicine items (i.e. NSAIDs, corticosteroids and traditional DMARDs) before they may be treated with biological medicine items.

NSAIDs, selective COX-2 inhibitors and corticosteroids are mainly used as adjunctive therapies since they offer a quick onset of symptom relief. NSAIDs, such as ibuprofen and naproxen, temporarily relieve symptoms but do not affect the underlying disease process. NSAIDs are not appropriate for monotherapy and should be used only in conjunction with a DMARD. Corticosteroids should be used only on a short-term basis, and only when other simpler approaches fail. When used in conjunction with DMARDs, corticosteroids may have certain safety advances (Rossiter, 2010:393). DMARDs on the other hand have the ability to alter the disease outcome and slow radiographic progression, and should be started as soon as the diagnosis of RA is certain. DMARDs, such as methotrexate or cyclosporine, should be regularly adjusted with the aim of suppressing disease activity. DMARDs are commonly given in combination with each other (2 or more DMARDs simultaneously). Prescribers may initiate treatment with a single treatment and add agents at 3-6 monthly intervals, or start with 3-4 agents and reduce the number of agents progressively (Rossiter, 2010:395). The older DMARDs, however, have toxic profiles, and patients are compelled to alternate therapies after a period of time (Hellmann & Imboden, 2008:722). The traditional RA drugs used as adjunctive therapies included in this group are listed in Table 2.12, while Table 2.13 is a summary of the traditional DMARDs used to treat RA. Both tables were compiled from Rossiter (2010:386-398) and Wagner *et al*. (2004:588-594).

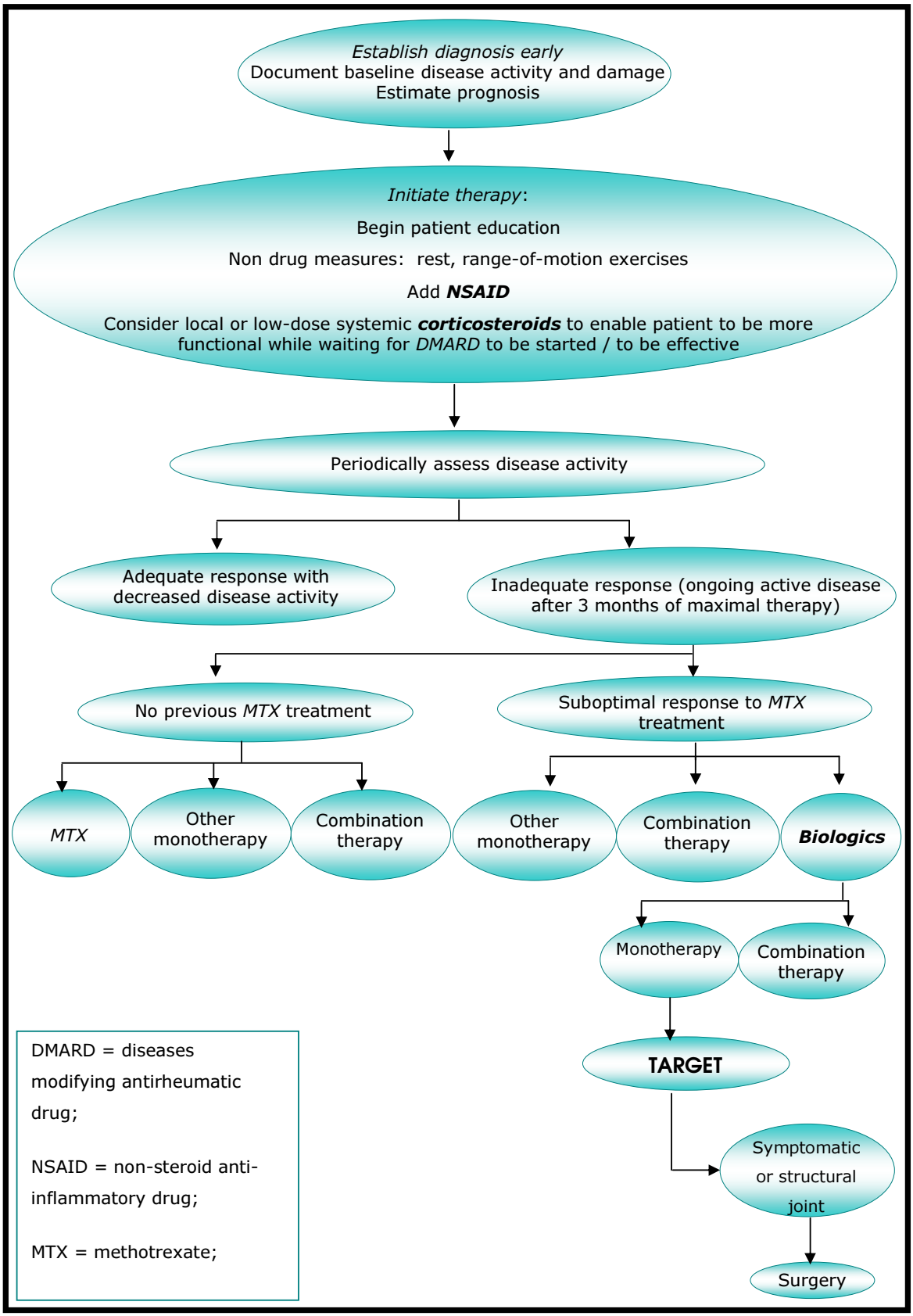

Figure 2.13 Treatment algorithm of RA (Adapted from Cohen *et al*., 2006:S31; SA, 2003:106)

Table 2.12 Traditional antirheumatic medicines used as adjunctive therapies (Rossiter, 2010:386-398; Wagner *et al*., 2004:588-594)

Class/group	***Drug name***	***Mechanism of action***	***Side effects***
NSAIDs		NSAIDs inhibit the enzyme cyclo-oxigenase (COX) which is responsible for converting arachidonic acid to prostaglandins. Prostaglandins play important roles in promoting inflammation. When COX is inhibited by NSAIDs, prostaglandins cannot form and inflammation is prohibited.	• ***Gastrointestinal side effects*** o Gastric ulceration, perforation, gastrointestinal hemorrhage. • ***Renal side effects*** o Interstitial nephritis, nephrotic syndrome, prerenal azotemia, aggravation of hypertension. • ***Platelet side effects*** o Prolongs bleeding time.
Acetic acid derivatives	Diclofen, indometacin, ketorolac		
Oxicams	Lonoxicam, meloxicam, piroxicam, fenoxicam		
Propionic acid derivatives	Ibuprofen, naproxen		
Fenamates	Mefenamic acid		
Other	Nabumetone, phenylbutazone		
COX-2 INHIBITORS		COX-2 inhibitors work in the same way as NSAIDs, but selectively inhibit the COX-2 isomer of the cyclo-oxigenase enzyme. Selective COX-2 inhibitors are as effective as NSAIDs in treating RA. <u>*Adult dose*</u>: Maximum 200 mg per day.	• ***Cardiovascular events*** o Associated with long-term use of COX-2 inhibitors. • COX-2 inhibitors are ***less likely*** to cause upper gastrointestinal side-effects and do not inhibit platelet function.
Coxibs	Celecoxib, etoricoxib, parecoxib		
CORTICOSTEROIDS		Low-dose corticosteroids produce a rapid anti-inflammatory effect in RA, and slows the rate of bone destruction by suppressing the immune system. Long-term use of corticosteroids is limited by multiple side- effects. <u>*Adult dose*</u>: Maximum 10 mg daily.	• ***Long-term corticosteroid use side-effects:*** Adrenal atrophy, inadequate cortisol secretion in response to stress, osteoporosis, Cushing's syndrome, diabetes, water retention, hypertension, hypokalemia, muscle weakness, euphoria, depression, thinning skin, glaucoma, GIT problems.
Systemic glucocorticoids	Prednisolone, prednisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, corticotropin		
Local corticosteroid injections (limited to 4 injections a year)	Preparations of methylprednisolone, betamethasone, dexamethasone		
COX-2 = cyclo-oxygenase-2; GIT = gastrointestinal tract; NSAIDs = non-steroid anti-inflammatory drugs.			

Table 2.13 Traditional DMARDs used in the treatment of RA* (Rossiter, 2010:386-398; Wagner *et al*., 2004:588-594)

DMARD	*Mechanism of action*	*Dosage and administration*	*Important side-effects*
Methotrexate	• Initial synthetic DMARD of choice for RA patients. • Is a folic acid antagonist that binds to the catalytic site of DHFR. • Inhibits AICAR transformylase and thymidylate synthetase at the low doses used in rheumatic diseases; it also has secondary effects on polymorphonuclear chemotaxis. • Considered the first DMARD of choice in the treatment of RA; used in up to 60% of patients. Much lower doses of MTX are necessary to treat RA than for cancer.	• *Initial dose*: 7.5 mg weekly, orally. • No response after *one month*: 15 mg once a week. • *Maximum dose*: 25 mg weekly. • Folic acid helps prevent MTX induced myelosuppression.	• Gastric irritation and stomatitis. • Interstitial pneumonitis (severe and life threatening). • Hepatotoxicity (liver function tests every 4-6 weeks). • Cytopenia and infection.
Sulfasalazine	• Second-line agents for RA. • Sulfasalazine is metabolised in the GI tract by intestinal bacteria to sulfapyridine and 5-ASA. Sulfapyridine is believed to be the key metabolite involved in treating RA. • Decreases in IgA and IgM have been observed in patients treated with sulfasalazine, together with a suppression of T cell responses and *in vitro* B cell proliferation.	• *Initial dose*: 0.5 g twice daily, orally. • Increased by 0.5 g each week until patient improves, or until daily dose is 3 g or 40 mg/kg.	• Neutropenia. • Thrombocytopenia. • Hemolysis (in patients with G6PD deficiency). • Blood counts every 2-4 weeks for the first 3 months, and then every 3 months are necessary.
Cyclosporin	• Inhibits IL-1 and IL-2 receptor production, and secondarily inhibits macrophage-T cell interaction and T cell responsiveness through regulation of gene transcription. • Also affects T cell-dependent B cell function. • Low-dose cyclosporin in combination with methotrexate may have enhanced disease modifying effects.	• *Initial dose*: 2.5 mg/kg/day in 2 divided doses, increased *after 6 weeks* up to 4 mg/kg/day. • *Maintenance*: Titrate to lowest effective dose, decrease by 0.5 mg/kg monthly or bi-monthly. • Discontinue use if no response after 3 months.	• Nephrotoxicity (dose related), hyperkalemia, hyperuricaemia, hypomagnesaemia, hyperlipid-aemia, microangiopathic hae-molytic anemia, hypertension, nausea, headache, hepato-toxicity, neurotoxicity, gingival hyperplasia, hirsutism, lympho-proliferative and

Table 2.13 Traditional DMARDs used in the treatment of RA *(continued)*

			skin disorders.
Gold	• Gold's major mode of action possibly lies in the altering of the morphology and functional capabilities of human macrophages. • This results in the inhibition of monocyte chemotactic factor-1, IL-8, IL-1β production, and vascular endothelial growth factor.	*Gold is no longer available in South Africa because of its significant toxicity profile and weak antirheumatic effects.*	
Chloroquine	• The mechanism of the anti-inflammatory action of is unclear. • It has been proposed that the suppression of T cell responses to mitogens, decreased leukocyte chemotaxis, stabilisation of lysosomal enzymes, inhibition of DNA and RNA synthesis, or the trapping of free radicals may be possible mechanisms of action.	• *Initial dose*: 150-300 mg daily. • After *7-10 days*: 150 mg daily. • *After remission is obtained*: a 5-days-a week regimen of 2.4 mg/kg.	• ***Common side-effects***: GIT effects, skin rash, pruritis, headache, vertigo. • ***Rare side-effects***: Ototoxicity, blood dyscrasias, cardiovascular effects, irreversible ocular damage.
Azathioprine	• Suppresses inosinic acid synthesis, B cell and T cell function, immunoglobulin production, and IL-2 secretion through its major metabolite, 6-thioguanine.	• *Initial dose*: 1-2.5 mg/kg/day. • If no response after 3 months – consider withdrawal.	• Myeloid suppression. • Thrombocytopenia. • Anemia.
Leflunomide	• Leflunomide is a prodrug of an inhibitor of pyrimidine synthesis.	• *Daily dose*: 20 mg as a single dose.	• Diarrhea, rash, reversible alopecia, hepatotoxicity.
Penicillamine	• A metabolite of penicillin and an analog of amino acid cystine. • Penicillamine is infrequently used today because of its toxicity.	*Penicillamine is no longer available in South Africa because of its significant toxicity profile and weak antirheumatic effects.*	
Minocycline	• Tetracycline antibiotic that reduces the swollen joint count and acute phase response in early RA, but does not impede the radiological progression of RA.	• *Daily dose*: 200 mg.	• Dizziness (in 10% of patients).

***Contains only the DMARDs included in the 9th edition of the SAMF, as it is the most accurate reference to the drugs currently indicated for use in SA.**

5-ASA = 5 amino salicylic acid; AICAR = aminoimidazolecarboxamide; DHFR = dehidrofolate reductase; DMARD = disease-modifying antirheumatic drug; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; Ig = immunoglobulin; IL = interleukin; RA = rheumatoid arthritis.

- *Biological RA therapies*

Senolt *et al*. (2009:1) are of the opinion that biological therapy has become a cornerstone in the treatment of RA cases where there is an inadequate response to standard DMARDs, since biologic agents target specific components of the immune system believed to play an essential role in the etiology and the sustenance of the disease process. However, biological RA therapies may not just be used by any patient with RA. The South African Rheumatoid Arthritis Association (SARAA) has a set of criteria which determines whether RA patients qualify to use TNF-alpha inhibitors. The entry criteria for use of anti-TNF agents in RA set by the SARAA are the following (SARAA, 2009:2):

- Patients must fulfill ACR criteria for RA. High disease activity (SDAI > 26) or moderate active disease (SDAI ≥ 11 – 26, and a motivation must accompany the application).

- Patients must have a history of use of at least three DMARDs used consecutively or in combination over six month periods at maximum tolerated doses, and MTX must be one of the DMARDs unless contra-indicated and leflunomide should be used if appropriate.

- Patients with three or more poor prognostic features (i.e. strongly positive RF factor, HAQ ≥ 1.5, patients older than 60 years at age of onset, radiographic erosion within two years of disease, extra-articular diseases such as nodules etc.) can also qualify for TNF-alpha inhibitors.

Only once RA patients met these criteria, are they registered with the SARAA biologics registry and permitted to use biological therapies (SARAA, 2009:2). Table 2.14 shows which biological agents were available for RA treatment by 2009, but only those RA biologics available in South Africa and available on the research data were discussed in short

Table 2.14 FDA approved biologics for RA (Senolt *et al*., 2009:1)

RA biologic		***Effect***	***Available in SA[#]***
TNF-α INHIBITORS	***Infliximab (Revellex®)***	Chimeric monoclonal Ab	Yes
	Etanercept (Enbrel®)	TNF-α receptor	Yes
	Adalimumab (Humira®)	Human monoclonal Ab	Yes
IL-1 INHIBITOR	***Anakinra (Kineret®)***	IL-1 receptor antagonist	No
IL-6 INHIBITOR	***Tocilizumab (Actemra®)***	Humanised monoclonal anti-IL-6 receptor Ab	No
B-LYMPHOCYTE DEPLETION	***Rituximab (MabThera®)***	Monoclonal anti-CD20 Ab	Yes
INHIBITION OF COSTIMULATION	***Abatacept (Orencia®)***	Fusion protein CTLA-4 with Ig	No
[#]According to 2010 MIMS.			

- **TNF-alpha inhibitors**

As it has already been deliberated, TNF-α is one of the cytokines believed to play a strategic role in the inflammation and joint damage present in RA. High levels of TNF-α is present in the synovial fluids of patients with RA; where it binds to its receptor (present on the cell membranes of various cells), and initiates a signal transduction cascade that results in the destruction of bone and cartilage (Carteron, 2000:316). The targeting of TNF-α as a pro-inflammatory cytokine, has therefore become a strategic basis for developing therapies to treat RA (Carteron, 2000:315).

According to De Vries-Bouwstra *et al*. (2005:745), TNF-α inhibitors have the ability to directly suppress disease activity, slow or stop radiological damage progressions, and prevent further loss of quality of life. Treatment compliance of TNF-α inhibitors is also favourable since they exhibit high clinical effectiveness, without showing many adverse events (De Vries-Bouwstra *et al*., 2005:745).

The TNF-α inhibitors currently approved in South Africa for treating RA are etanercept, infliximab and adalimumab, which are discussed below. The dosages and outcomes are specific to the use of the particular biologic immunomdulator in rheumatoid arthritis (Rossiter, 2010:398).

∂ **Etanercept**

× *Pharmacological classification*

Etanercept is a human recombinant version of the soluble p75 TNF receptor that is linked to the Fc receptor of human IgG subclass 1 (Immunex corporation, 2003). Etanercept became the first biological agent approved by the FDA for the treatment of RA in 1998 (Amgen & Wyeth Pharmaceuticals, 2009).

ATC classification: L04AB01

Antineoplastic & Immunomodulating agents: Immunosuppressants (WHO, 2009).

MIMS classification: Group 4

Musculo-skeletal agents: Group 4.6 Others (Snyman, 2010:81).

× *Mechanism of action*

Etanercept is a TNF-α inhibitor, which means that it competitively inhibits TNF-α to bind to its receptors on the surface of cells, and thereby inhibits TNF-α-induced proinflammatory activity in the joints of RA patients. Etanercept also acts as a cytokine "carrier". It renders the proinflammatory cytokine TNF-α, which is released in the body by activated macrophages and T cells, biologically inactive (Immunex corporation, 2003).

× *Dosage and administration*

The guidelines set by the SARAA states that dosing of TNF-alpha inhibitors should be based on the manufacturer's recommendations (SARAA, 2009:4). Thus:

Adult dose: 25 mg injected subcutaneously twice weekly (Rossiter, 2010:398). This weekly dose of 50 mg may also be given as a single 50 mg injection, or as two 25 mg injections at about the same time (Sweetman, 2010). Etanercept can be taken alone or in combination with methotrexate (Amgen & Wyeth Pharmaceuticals, 2009).

Administration in children: Etanercept is indicated for active polyarticular juvenile idiopathic arthritis in children over 4 years of age. 0.4 mg/kg (up to a maximum of 25 mg) is given subcutaneously twice a week at intervals of 3 or 4 days (Rossiter, 2010:398; Sweetman, 2010). Sweetman (2010) states that use of etanercept should be discontinued if there is no response after 12 weeks of therapy, whereas the exit criteria of the SARAA states that the use of TNF-alpha inhibitors should be stopped if there is failure to achieve adequate improvement, or failure to achieve a low disease rate (SARAA, 2009:3).

× *Outcome*

Etanercept has been shown to be effective in about 2 out of 3 adults with RA (Amgen & Wyeth Pharmaceuticals, 2009). Improvement with etanercept is extremely rapid, as it has shown to begin working within 2 weeks after the first injection, with most patients receiving benefit within 3 months. Amgen & Wyeth Pharmaceuticals (2009) furthermore indicated that, 55% of RA patients have no progression of joint damage while being treated with etanercept, but symptoms do however return after therapy has been discontinued.

- **Infliximab**

× *Pharmacological classification*

Infliximab is a chimeric monoclonal antibody to TNF-α. Chimeric monoclonal antibodies are composed from 25% mouse and 75% human antibodies (Centocor, Inc., 2006).

ATC classification: L04AB01

Antineoplastic & Immunomodulating agents: Immunosuppressants (WHO, 2009).

MIMS classification: Group 24

Immunological agents: Group 24.1 Immuno-suppressants (Snyman, 2010:344).

× *Mechanism of action*

Infliximab neutralises the biological activity of TNF-α. It acts by binding to soluble and possibly membrane-bound TNF-α with high affinity (Centocor, Inc., 2006). The complex that is formed between infliximab and soluble TNF-α prevents TNF-α from interacting with cell surface receptors p55 and p75. This results in down-regulation of macrophage and T cell function – both of which play a key role in the pathogenesis of RA (Wagner *et al*., 2004:592).

× *Dosage and administration*

Adult dose: 3mg/kg in 250ml 0.9% sodium chloride solution over at least 2 hours, as an intravenous injection, followed by 3mg/kg at 2 weeks and 6 weeks after the first infusion, and every 8 weeks thereafter (Rossiter, 2010:398; Sweetman, 2010).

The guidelines of the South African Rheumatism and Arthritis association state that infliximab must be infused at a supervised day facility with appropriately trained staff and resuscitation equipment available (SARAA, 2009:2). Infliximab may be used alone as monotherapy, but is mostly used in conjunction with methotrexate (Carteron, 2000:319; Sweetman, 2010). According to Sweetman (2010), a clinical response is usually achieved within 12 weeks of starting treatment. Patients, who respond inadequately during this period, may increase the dose to a maximum of 10 mg/kg every 8 weeks. Therapy should be reconsidered if patients still fail to respond within 12 weeks of the

altered dose, and withdrawn if an adequate response is not achieved within 6 months of starting the treatment.

Administration in children: Infliximab is not indicated for use in children with active polyarticular juvenile idiopathic arthritis (Rossiter, 2010:398; Sweetman, 2010).

× *Outcome*

Treatment of RA with infliximab reduces infiltration of inflammatory cells into inflamed areas of the affected joints. It has also been shown that infliximab reduces expression of molecules that mediate cellular adhesion, chemoattraction, and tissue degradation (Centocor, Inc., 2006). Treatment with infliximab alone thus does demonstrate clinical improvement of RA symptoms in clinical trial subjects receiving this treatment, but it has also been shown that anti-infliximab antibodies develop in patients receiving infliximab infusions, which may cause a possible decrease in the efficacy of infliximab over time. Infliximab in combination with methotrexate on the other hand, results in significant improvements compared to methotrexate alone, as well as a decrease in the number of anti-infliximab antibodies developed. This option, however, is not appropriate for long-term use in patients who cannot tolerate methotrexate (Carteron, 2000:319).

∂ **Adalimumab**

× *Pharmacological classification*

Adalimumab is a human recombinant IgG anti-TNF-α antibody (Abbott laboratories, 2010).

ATC classification: L04AB01

Antineoplastic & Immunomodulating agents: Immunosuppressants (WHO, 2009).

MIMS classification: Group 24

Immunological agents: Group 24.1 Immunosuppressants (Snyman, 2010:344).

× *Mechanism of action*

Adalimumab forms a complex with soluble TNF-α and prevents its interaction with cell surface receptors p55 and p75, through which macrophage and T cell function is down-regulated (Wagner *et al*., 2004:592). Adalimumab also acts as a biological response modifier as it modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (Abbott laboratories, 2010).

× *Dosage and administration*

Adult dose: 40 mg as a subcutaneous injection every 2 weeks (Rossiter, 2010:398). According to Sweetman (2010), some patients may benefit from increasing the dose to 40 mg every week. If an adequate response is not achieved within 12 weeks of starting treatment, therapy with adalimumab should be discontinued (Sweetman, 2010).

Adalimumab should preferably be used in combination with methotrexate, unless treatment with methotrexate is contraindicated, or not well tolerated. Other DMARDs, NSAIDs and glucocorticoids may also be continued during adalimumab therapy to manage symptoms (Rossiter, 2010:398).

Administration in children: Adalimumab may be used in children as young as 4 years old to treat active polyarticular juvenile idiopathic arthritis. Children weighing between 15 kg and 30 kg are given 20 mg subcutaneously every other week, while children weighing more than 30 kg are given 40 mg every other week (Sweetman, 2010).

× *Outcome*

Abbott laboratories (2010) reported a rapid decrease in levels of acute phase reactants of inflammation and cytokines in the serum of RA patients after treatment with adalimumab. After adalimumab administration, there was also a decrease in serum levels of matrix metalloproteinases that produce tissue remodelling responsible for cartilage destruction (Abbott laboratories, 2010).

- **B-lymphocyte depletion agent**

According to Chaiamnuay and Bridges (2005:203), B cells have several possible key roles in the pathogenesis of RA. Although the precise contribution of B cells to the immunopathogenesis of RA is not well characterised, various mechanisms by which B cells may play a part in the disease process have been proposed. B cells act as APCs and provide co-stimulatory signals required for CD4+ T cell activation and effector functions; they secrete proinflammatory cytokines such as TNF-α and chemokines; and they produce RF and other autoantibodies.

The relative importance of each of these mechanisms is unknown, but it is becoming increasingly clear that through multiple mechanisms, B cells potentially have a central role in RA, and are thus an appropriate target for therapeutic intervention (Shaw *et al*., 2003:ii55).

∂ **Rituximab**

× *Pharmacological classification*

Rituximab is a chimeric anti-CD20 monoclonal antibody, directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Rituximab's original indication was for non-Hodgkin's lymphoma and a few other cancers. It was not until recently that rituximab was used in the treatment of RA (Biogen Idec Inc. & Genentech Inc., 2003; Sibilia *et al.,* 2008:526).

ATC classification: L01XC02

Antineoplastic & Immunomodulating agents: Antineoplastic agents (WHO, 2009).

MIMS classification: Group 26

Biological agents: Group 26 (Snyman, 2010:351).

× *Mechanism of action*

Rituximab selectively depletes peripheral B cells by targeting a unique cell-surface marker found on B cells known as CD20 (Tak, 2010:1). It then recruits the body's natural defences to attack and kill the marked B cells (Roche, 2010).

Rituximab's mechanism of action has three alleged components that contribute to its B cell depletion properties:

- Antibody dependent cell mediated cytotoxicity, in which NK cells, macrophages and monocytes bound to surface CD20.
- Complement dependent cytotoxicity, induced by complexed rituximab bound to surface CD20. This results in activation of the complement cascade and generation of the membrane attack complex, causing CD20+ B cell lysis.
- Promotion of CD20+ B cell apoptosis (Shaw *et al.*, 2003:ii56).

× *Dosage and administration*

Adult dose: 1000 mg as an intravenous infusion, followed by a second dose of 1000 mg two weeks later. 100 mg of intravenous methylprednisolone given 30 minutes prior to the rituximab infusion decreases the rate and severity of acute infusion reactions (Rossiter, 2010:398). Rituximab is given in combination with methotrexate (Sweetman, 2010).

Administration in children: Rituximab is not indicated for use in children with active polyarticular juvenile idiopathic arthritis (Sweetman, 2010).

× *Outcome*

According to Tak (2010:4), rituximab demonstrates the ability to slow structural joint damage progression in RA. Shaw *et al.* (2003:ii58) elaborate on this by stating that the clinical data to date indicate that after only a single treatment course, rituximab produces high levels of unremitting efficacy in RA, that coincide with a profound and long-lasting peripheral depletion of CD20+ B cells. Shaw *et al*. (2003:ii57) state that it has been indicated that a combination of rituximab with methotrexate or cyclophosphamide produces the highest levels of response.

2.7.2 Crohn's disease

2.7.2.1 Definition

Myers (2006:482) defines Crohn's disease as *"a chronic inflammatory gastrointestinal disease that can affect any part of the gastrointestinal tract"*. McQuaid (2008:545) states that Crohn's disease is typically characterised by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus, but favours the terminal ileum and proximal colon.

2.7.2.2 Disease prevalence by age and gender

According to Longmore *et al*. (2007:266), approximately 50 to 100 people out of 100 000 are affected by Crohn's disease, with the risk of disease three- to fourfold higher among smokers. Kappelman *et al*. (2007) reported that the prevalence of Crohn's disease in children younger than 20 years was 43 cases per 100,000 children, and the prevalence in adults was 201 per 100,000 people. The number of men and women affected is equal.

2.7.2.3 Clinical presentation

Crohn's disease typically presents with symptoms of diarrhea, abdominal pain, and weight loss; although symptoms like fever, malaise, and anorexia can also be present with active disease.

Intra-intestinal signs are established during a physical examination and include signs such as aphthous ulceration; abdominal tenderness; right iliac fossa mass; perianal abscesses; and anal or rectal strictures.

Extra-intestinal signs may also be present and include clubbing, conjunctivitis, large joint arthritis, ankylosing spondylitis, fatty liver, renal stones, osteomalacia and malnutrition, among others (Longmore *et al*., 2007:266; McQuaid, 2008:547).

2.7.2.4 Diagnostic criteria

In order for a positive diagnosis of Crohn's disease to be made, several tests have to be carried out; including blood tests for several blood elements, taking stool samples, doing a sigmoidoscopy or rectal biopsy, small bowel enema, barium enema, capsule endoscopy or a colonoscopy (McQuaid, 2008:547). Results of these tests will determine whether a patient has Crohn's disease. Markers of activity for Crohn's disease also contribute to its diagnosis, and include low hemoglobin and albumin levels, with an increased white blood cell count; C-reactive Protein (CRP); and erythrocyte sedimentation rate (Longmore *et al*., 2007:266).

2.7.2.5 Desired outcome

The goals of Crohn's disease therapy include the following: resolution of inflammation and healing of the mucosa; restoration and preservation of good nutrition and growth; maintenance of a good quality of life; closure of fistulae; prevention of complications such as strictures, abscesses and cancer; and prevention of post-operative recurrence. According to Helper (2009:371), most of these goals are now achievable with medical therapy while some remain difficult to treat.

2.7.2.6 Pharmacological treatment

The selection of therapies for Crohn's disease has expanded significantly over the past 30 years. For many decades the management of Crohn's disease was dominated by the use of corticosteroids and surgery, but the medical management of this disease has however shifted. Presently, the focus of Crohn's disease management is on therapeutic options that include the use of immunomodulatory and biologic agents for induction and maintenance of remission, and surgery is mainly reserved for treating complications such as stricture, perforation, abscesses and cancer (Helper, 2009:371).

- *Traditional Crohn's disease therapies*

McQuaid (2008:545) states that despite extensive research, there are no specific therapies for Crohn's disease. The mainstay therapies are the 5-aminosalicylic acid (5-ASA)

derivatives, corticosteroids, immunomodulating agents (like mercaptopurine and azathioprine), methotrexate, and biologics like infliximab and adalimumab.

According to Rossiter (2010:59), corticosteroids are the basis of therapy for acute flares of Crohn's disease, but seeing that they are ineffective in maintaining remission, corticosteroids are not generally indicated for maintenance of chronic active Crohn's disease. Maintenance therapy is, however, effectively achieved with immunosuppressive agents. The use of immunosuppressive agents is unfortunately limited by their potential to cause serious adverse effects, particularly in the bone marrow. Nonetheless, immunosuppressive therapy is presently the mainstay of therapy in maintaining remission of complicated Crohn's disease (Helper, 2009:371).

Table 2.15 (Longmore *et al.*, 2007:266; McQuaid, 2008:545; Rossiter, 2010:59) contains the most important therapies used in the treatment of Crohn's disease, and Figure 2.14 shows the current treatment algorithm of Crohn's disease as published in the South African Government Gazette (SA, 2003:71).

Table 2.15 Traditional therapies for Crohn's disease* (Longmore *et al*., 2007:266; McQuaid, 2008:545; Rossiter, 2010:59)

Drug [†]	***Mechanism of action***	***Indication / Dosage***	***Side-effects***
Treatment of acute flares			
Corticosteroids	Corticosteroids suppress many aspects of the inflammatory process, as well as suppression of immunological responses involved in chronic inflammatory conditions like Crohn's disease.		***Most common side effects:*** Mood changes, insomnia, hypertension, weight gain, edema, elevated serum glucose levels, Cushing's syndrome.
Prednisolone / methylprednisolone		*Mild attacks*: 30 mg/day orally for one week, then 20 mg/day for one month; reduce dosage with 5 mg every 2-4 weeks and stop treatment when parameters are normal.	
Hydrocortisone / methylprednisolone		*Severe attacks*: 100 mg IV over 6 hours.	
Sulfasalazine and other 5-ASA preparations *(mesalazine, olsalazine)*	Sulfasalzine splits into sulfapyridine and 5-ASA. 5-ASA has anti-inflammatory properties which contribute to the drug's benefits.	Mainly used in maintenance of remission, but has a role in acute disease. *Initial dose*: 4 g/day orally in divided doses, reduced to 2 g /day to maintain remission.	Side-effects are ***uncommon***, but may include: nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis.
Treatment to maintain remission			
Immunosuppressive therapies	Azathioprine and mercaptopurine act by suppressing the immune responses responsible for inflammation associated with CD.		Myeloid suppression, thrombocytopenia, anaemia, severe red blood cell megaloblastosis, anaphylaxis.
Azathioprine		*To maintain remission*: 2 – 2.5 mg/kg/day.	
Mercaptopurine		*To maintain remission*: 1 – 1.5 mg/kg/day.	
Methotrexate (MTX)	MTX has anti-inflammatory properties, including inhibition of expression of TNF-α in monocytes and macrophages, at low doses.	*To maintain remission*: 15 mg/week IM or SC. May also be given orally.	Myeloid suppression, gastric irritation, stomatitis, interstitial pneumonitis, hepatotoxicity, cytopenia and infection.
Metronidazole / Ciprofloxacin	*Mechanism of action in CD is uncertain.*	Beneficial in patients with perianal fistulas. Long term use of metronidazole may be limited by the development of peripheral neuropathy and concern over its possible carcinogenic potential.	***Metronidazole:*** nausea, anorexia, headache, metallic taste in mouth. ***Ciprofloxacin:*** generally well tolerated, but GIT problems may occur.

***Contains only the therapies indicated for Crohn's disease in South Africa. [†]Rossiter, 2010:59.**

5-ASA = 5-aminosalicylic acid; CD = Crohn's disease; IM = intramuscular; IV = intravenous; SC = subcutaneous.

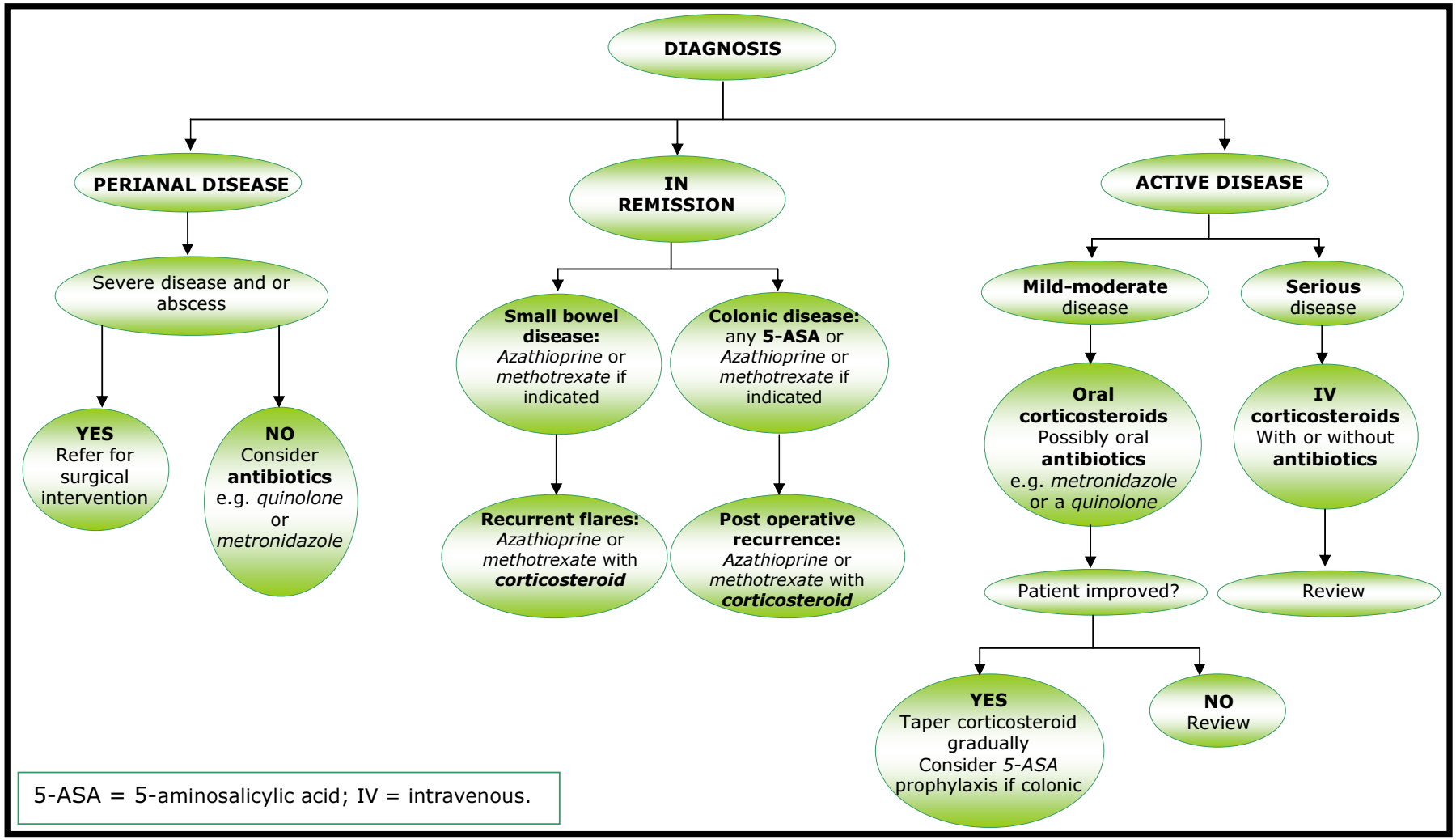

Figure 2.14 Treatment algorithm of Crohn's disease (SA, 2003:71)

- *Biological Crohn's disease therapies*

The treatment algorithm for Crohn's disease as determined by the Minister of Health and published in the Government Gazette as part of the Medical Schemes Act (131/1998) does not currently include biologics (SA, 2003:71). Biologics are, however, prescribed for patients who do not respond to the standard therapies and for whose health it would be detrimental to refuse the use of biologics (Council for Medical Schemes, 2005:4). There are only two biological medicines approved for Crohn's disease in South Africa. They are the TNF-α inhibitors adalimumab and infliximab (Rossiter, 2010:65).

Adalimumab

Adalimumab is indicated for the treatment of Crohn's disease where the disease is noncompliant to conventional therapies, and in patients who have lost response to, or cannot tolerate infliximab (Rossiter, 2010:59).

× *Pharmacological classification* and *mechanism of action*: refer to section 2.7.1.7, page 69.

× *Dosage and administration*

Adult dose: 160 mg as a subcutaneous injection at week 0 (4 injections daily or 2 injections daily for 2 consecutive days), 80 mg at week 2, followed by 40 mg every other week. Can be increased to 40 mg every week if necessary (Rossiter, 2010:65; Sweetman, 2010).

According to Sweetman (2010), an adequate response is usually achieved within 12 weeks of starting treatment. If no response is achieved within this period, therapy with adalimumab should be discontinued.

Administration in children: Adalimumab is not indicated for Crohn's disease in children (Sweetman, 2010).

× *Outcome*

The clinical efficacy and safety of adalimumab in patients with moderate to severe Crohn's disease has been demonstrated in four fundamental, randomised, double-blind trials. The trials were the CLASSIC-I, CLASSIC-II, GAIN and CHARM and trials respectively, and included over 1400 patients in total.

In the CLASSIC-I trial, adalimumab was considerably more effective for induction of remission in patients who had never before received anti-TNF therapy, than placebo (Sandborn *et al.*, 2007a:1232).

In the GAIN study, adalimumab was also shown to be more effective than placebo for induction of remission in patients who had either lost responsiveness or developed intolerance to infliximab (Sandborn *et al*., 2007b:829).

Results of the CHARM trial showed that maintenance therapy with adalimumab at a dose of 40 mg a week or every other week for up to 1 year was associated with drastically superior remission rates than placebo at weeks 26 and 56 among patients who responded to open-label adalimumab induction (Feagan *et al*., 2008:1493). Furthermore, the number of adalimumab recipients who achieved corticosteroid-free remission and had complete fistula closure at the end of the trial, greatly exceeded the number of placebo recipients (Feagan *et al*., 2008:1493).

The CLASSIC-II trial, which was an extension of the CLASSIC-I trial, showed that patients, who were in remission after a short course of adalimumab and were randomised to receive up to 1 year's treatment with adalimumab at doses of 40 mg a week or every other week, were considerably more likely to remain in remission than those randomised to receive placebo (Sandborn *et al.*, 2007a:1232). The tolerability profile of adalimumab in patients with Crohn's disease was similar to the tolerability profile in patients with RA or other approved indications (Plosker & Lyseng-Williamson, 2007:125).

- **Infliximab**

Infliximab has greatly influenced the management of Crohn's disease. It is indicated for the treatment of refractory luminal disease, as well as fistulising Crohn's disease (Rossiter, 2010:59). Maintenance and remission is achieved through long-term continuance with regular scheduled infusions (Rossiter, 2010:59).

× *Pharmacological classification* and *mechanism of action*: refer to section 2.7.1.7, page 68.

× *Dosage and administration:*

Adult dose: *For active Crohn's disease*: 5 mg/kg infliximab in 250 ml 0.9% sodium chloride solution given as an intravenous infusion over 2 hours, as a single dose. An induction regimen of 3 doses of 5 mg/kg at 0, 2 and 6 weeks are preferable to a single infusion for both luminal and fistulising Crohn's disease. This is followed by 8-weekly dosing at 5 mg/kg whenever possible.

For fistulising Crohn's disease: an intravenous infusion of 5 mg/kg infliximab in 250 ml 0.9% sodium chloride solution over at least 2 hours, followed by 5 mg/kg at 2 weeks and 6 weeks after the first infusion (i.e. a course of three doses) (Rossiter, 2010:65; Sweetman, 2010).

Patients who do not achieve clinical benefit after the initial 3 doses are considered unresponsive and treatment is withdrawn (Sweetman, 2010).

Administration in children: Infliximab is licensed for use in moderate to severe, active Crohn's disease in children 6 years and older who do not respond adequately to conventional therapy. Doses are the same as for adults (Sweetman, 2010).

× *Outcome:*

According to Centocor Inc. (2006), treatment of Crohn's disease with infliximab reduces infiltration of inflammatory cells and TNF-α production in inflamed areas of the intestine, and reduces the portion of mononuclear cells from the lamina propria able to express TNF-α and interferon.

2.7.3 Multiple sclerosis (MS)

2.7.3.1 Definition

MS is a chronic inflammatory condition of the central nervous system, defined as a *"progressive disease characterised by disseminated demyelination of nerve fibers of the brain and spinal cord"* (Fisher *et al*., 2009:318; Myers, 2006:1234).

2.7.3.2 Disease prevalence by age and gender

According to Fisher *et al.* (2009:318), MS mostly affects young adults and is increasing in prevalence and incidence. Calabresi (2004:1935) states that MS typically presents in adults between the ages of 20 and 45.

Prevalence of MS is very variable as it is more common in areas with a mild climate (Longmore *et al*., 2007:488). For example: prevalence of MS in England is approximately 42 or more people per 100,000, whereas in Scotland, more or less 200 out of every 100,000 people are affected by MS. MS is rarer in Black Africa and Asia than in the United Kingdom, where the lifetime risk for MS is about 1:1000. The ratio of women to men burdened by MS is approximately 2:1, with the mean onset age of MS being 30 years (Longmore *et al*., 2007:488).

2.7.3.3 Clinical presentation

MS begins slowly, usually in young adulthood, and continues throughout life with periods of exacerbation and remission, that after numerous relapses, cause permanent neurologic deficits (Fisher *et al*., 2009:318). The presentation and course of MS varies significantly, but it is generally marked by recurrent attacks of neurologic dysfunction that are signified by demyelinating lesions or plaques throughout the brain and spinal cord of the CNS (Fisher *et al*., 2009:318). Presentation of MS is usually monosymptomatic.

The first signs of MS are paresthesias, or abnormal sensations in the extremities or on one side of the face, which may present as unilateral optic neuritis (pain in eye movement and rapid deterioration in central vision) or numbness or tingling in the limbs. Other early signs include muscle weakness, vertigo, and visual disturbances, such as nystagmus, double

vision, and partial blindness. Later in the course of disease there may be extreme emotional lability, ataxia, abnormal reflexes, and difficulty in urinating (Myers, 2006:1234). Even though it is uncommon, more than one symptom may sometimes be present (Longmore *et al*., 2007:488).

2.7.3.4 Diagnostic criteria

The diagnosis of MS is difficult to make, since many other conditions affect the nervous system and produce similar symptoms. The diagnosis is thus clinical, as it requires a demonstration of lesions spread over time and space (i.e. occur in different parts of the CNS at least three months apart), unattributable to other causes, supplemented by the findings of certain studies (Calabresi, 2004:1936; Longmore *et al*., 2007:488). A history of exacerbation and remission of symptoms, and the presence of higher than normal amounts of protein in cerebrospinal fluid are characteristic (Myers, 2006:1234).

2.7.3.5 Desired outcome

The treatment goals of MS are to improve a patient's quality of life by relieving symptoms caused by flare-ups, slowing the course of the disease as much as possible, and providing psychological support (Calabresi, 2004:1935). Therapies thus aim to manage the symptoms of MS, improve or sustain function, and preserve patients' quality of life (Crayton, 2006:445).

2.7.3.6 Pharmacological treatment

Treatment of MS has three main components: symptom management, relapse treatment to limit inflammation during an acute relapse and to shorten time to recovery, and disease modification (Crayton, 2006:445). Fisher *et al*. (2009:320) state that supportive therapy, such as physical therapy, occupational therapy, and counselling, may also be required.

- *Traditional MS therapies*

The first component of MS management consists of therapies aimed at relieving the symptoms. Table 2.16 ([1]Calabresi, 2004:1939; [2]Longmore *et al*., 2007:488) lists the therapies for each of the major symptoms of MS.

The second component of MS management is treating acute relapses. Adrenal corticosteroids are the mainstay of symptomatic relief for an acute relapse of MS, where of intravenous methylprednisolone forms the basis of relapse therapy (Rossiter, 2010:379). Corticosteroids work through immunomodulatory and anti-inflammatory effects, restoration of the blood brain barrier, and reduction of edema; they may also improve axonal conduction. Corticosteroid therapy shortens the duration of acute relapses and accelerates recovery, but has no effect in altering the disease process (Calabresi, 2004:1940).

Table 2.16 Symptomatic therapies for MS ([1]Calabresi, 2004:1939; [2]Longmore *et al*., 2007:488)

Symptom	***Therapy***
Spasticity[1,2]	Baclofen: 10 to 40 mg tds[1,2] Tizanidine: 2 to 8 mg tds[1,2] Gabapentin: 300 to 900 mg tds or qid[1] Dantrolene: 25 mg per 24 hours[2] Diazepam: 5 mg per 8-24 hours[2]
Pain & paroxymal disorders[1]	Gabapentin: 300 to 900 mg tds or qid[1] Carbamazepine: 100 to 600 mg tds[1] Amitriptyline: 10 to 150 mg per day at bedtime[1]
Bladder urgency[1,2]	Oxybutynin: 5 mg once daily to 20 mg per day[1,2] Tolterodine: 2 to 4 mg bd[1,2]
Depression[1]	SSRIs are preferred[1] Extended-release venlafaxine: 75 to 225 mg per day[1] Sustained-release bupropion: 150 mg bd[1] Amitriptyline: 10 to 150 mg per day at bedtime[1]
Fatigue[1]	Amantadine: 100 mg twice daily[1] Modafinil: 100 to 200 mg in the morning[1] and SSRIs[1]
bd = twice daily; tds = three times daily; qid = four times daily; SSRI = selective serotonin reuptake inhibitor.	

The third, and most important component of MS treatment, includes the disease-modifying therapies, which are immunomodulating agents targeted against the inflammatory component of the disease process to prevent or reduce the biological activity of MS (Fisher *et al*., 2009:320). Currently, there are six disease-modifying therapies approved by the FDA for use in relapsing/remitting MS. Table 2.17 (Fisher *et al.*, 2009:320) lists these agents. Immunosuppressants, like methotrexate and cyclophosphamide, may also be used on a short-term basis, to reduce the relapse rate of frequent relapses (Fisher *et al*., 2009:320).

The current treatment algorithm for MS as published in the Government Gazette (SA, 2005:19) is depicted in Figure 2.15. This algorithm gives a guideline as to the minimum medicines that have to be provided to an MS patient. The current algorithm does include the biologic immunomodulating agents, beta interferons, as potential agents for frequent relapses of secondary progressive MS.

According to Rossiter (2010:378), the only biologic immunomodulators indicated for relapsing/remitting MS in South Africa are the beta interferons and glatiramer acetate.

Table 2.17 Disease modifying therapies for MS: the immunomodulators (Fisher *et al.*, 2009:320)

Drug	***Therapeutic class***	***Indicated for MS in SA***
INF beta-1a (Avonex®)	Beta interferon (biologic agent)	YES
INF beta-1a (Rebif®)	Beta interferon (biologic agent)	YES
INF beta-1b (Betaferon®)	Beta interferon (biologic agent)	YES
Glatiramer acetate (Copaxone®)	Immunostimulant	YES
Mitoxantrone (Novantrone®)	Chemotherapeutic agent	NO
Natalizumab (Tysabrif®)	Monoclonal Ab (biologic agent)	NO
INF = interferon; Ab = antibody		

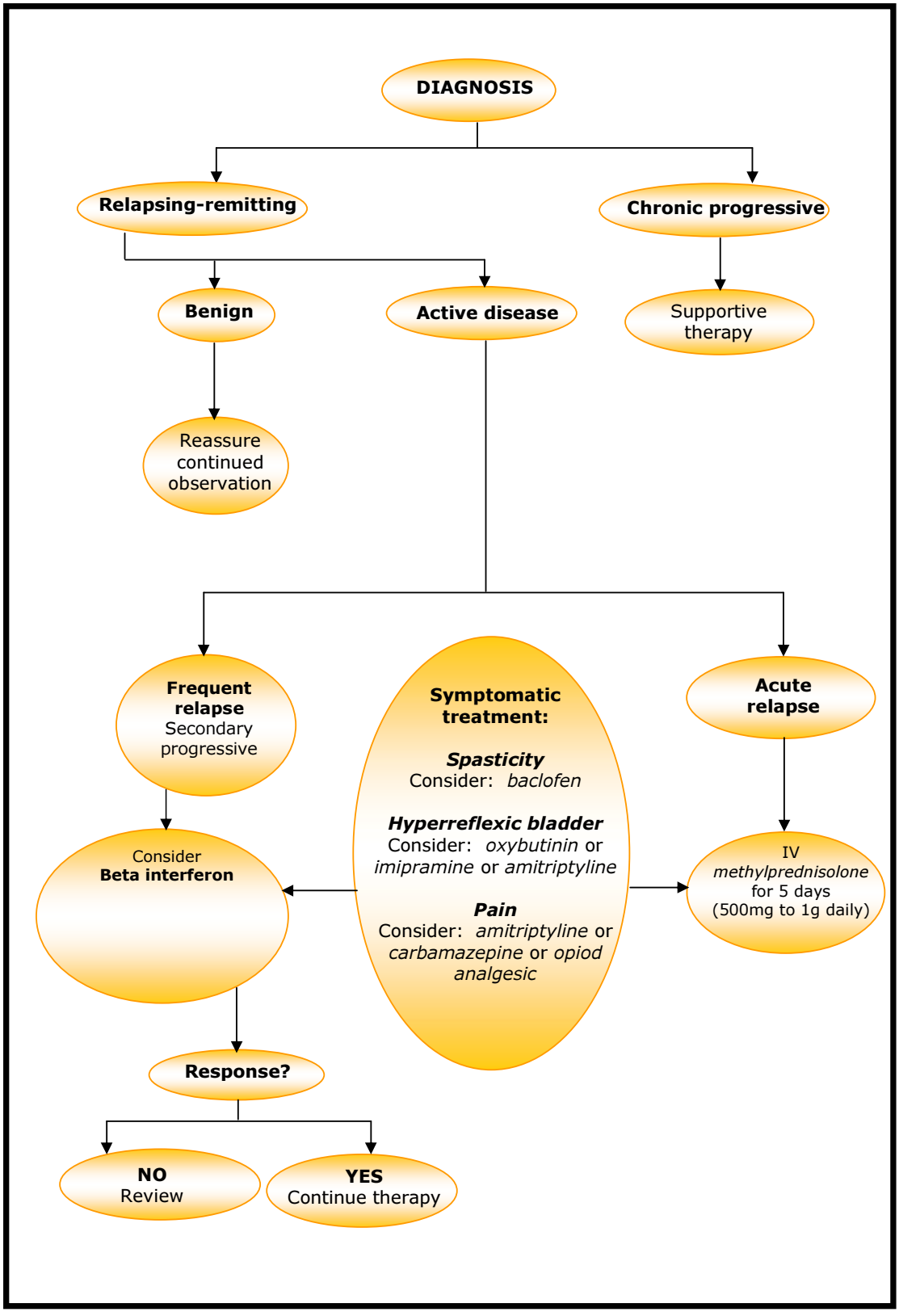

Figure 2.15 Treatment algorithm of multiple sclerosis (SA, 2003:100)

- *Biological MS therapies*

- **The beta interferons**

Interferons (IFNs) are a part of the body's non-specific immune system. IFNs occur naturally in the body and are biological glycoproteins that act as signalling proteins, and are used by the cells in the body to communicate with one another. Interferons are thus key communicators in the immune system (Bayer Healthcare Pharmaceuticals, 2009). They also play an important role in the first line of defence against viral infections, since they are induced at an early stage in viral infection, before the specific immune system has had time to respond (Hunt, 2009).

Interferons are generated *in vivo* by eukaryotic cells in response to a range of appropriate stimuli, and released into the surrounding medium. They then bind to receptors on target cells and induce transcription of approximately 20 to 30 genes in the target cells, which result in an anti-viral state in the target cells (Hunt, 2009).

Human interferons are divided into three main classes: interferon alpha, beta and gamma (Rossiter, 2010:378). The alpha and beta interferons are type I interferons. Interferon-alpha is a leukocyte interferon, and is produced by virus-infected leukocytes. Interferon-beta in contrast, is a fibroblast interferon which is produced by virus-infected fibroblasts, or virus-infected epithelial cells (Hunt, 2009). Type I interferons have considerably overlapping, but also distinct biologic activities. The bioactivities of interferons are mediated by their interactions with specific receptors on surfaces of human cells (Bayer Healthcare Pharmaceuticals, 2009).

Interferon-alpha (a family of about 20 related proteins) and interferon-beta are particularly potent as antiviral agents. They are not expressed in normal cells, but viral infection of a cell causes interferons to be made and released from the cell. Both DNA and RNA viruses induce interferon, although RNA viruses tend to induce higher levels. Double-stranded RNA produced during viral infection may be an important inducing agent. Other stimuli can also cause these interferons to be made: e.g. exogenous double-stranded RNA, lipopolysaccharide, and other components of certain bacteria (Hunt, 2009).

Interferon-alpha is mainly used in chronic viral hepatitis B, whereas interferon-beta is used in the treatment of relapsing-remitting MS (Rossiter, 2010:379). Interferon-beta is further divided into subgroups, of which interferon beta-1a and interferon beta-1b are the two main types of beta interferons relevant to this study.

∂ Interferon beta-1a *(Avonex® and Rebif®)*

× *Pharmacological classification*

Interferon beta-1 is a biological glycoprotein produced by means of rDNA technology. Both interferon beta-1a and interferon beta-1b are classified as interferons under "cytokines and immunomodulators" in the 9th edition of the SAMF, and grouped with the immunostimulants in therapeutic class L03A (Rossiter, 2010:378).

ATC classification: L03AB08

Antineoplastic & Immunomodulating agents: Immunostimulants (WHO, 2009).

MIMS classification: Group 24

Immunological agents: Group 24.2 Immunostimulants (Snyman, 2010:348).

× *Mechanism of action*

The mechanism of action of interferon beta-1 in patients with MS is uncertain (Bayer Healthcare Pharmaceuticals, 2009). Rossiter (2010:378) however asserts that interferon beta has the ability to reduce the inflammatory process that characterises the relapses of relapsing-remitting MS. It has thus been established that interferon beta-1 possesses not only antiviral properties, but also performs immunoregulatory activities.

It is believed that the biologic response-modifying properties of interferon beta-1 are mediated through its interactions with specific receptors found on the surface of human cells. The binding of interferon beta-1 to these receptors induces the expression of a number of gene products that are believed to be the mediators of the biological actions of interferon beta-1 (Schering (Pty) Ltd, 2005).

The immunomodulatory effects of interferon beta-1 furthermore include the enhancement of suppressor T cell activity, reduction of pro-inflammatory cytokine production, down-regulation of antigen presentation, and inhibition of lymphocyte trafficking into the central nervous system, that may contribute to its mechanism of action in MS (Bayer Healthcare Pharmaceuticals, 2009).

× *Dosage and administration*

Avonex® adult dose: 30 mcg intramuscular once weekly (Calabresi, 2004:1941). *Rebif*® adult dose: 22 to 44 mcg subcutaneously three times weekly (Calabresi, 2004:1941).

Administration in children: According to Snyman (2010:349), interferon beta is contra-indicated in children younger than 16 years of age.

× *Outcome*

According to Rossiter (2010:378), treatment of MS with beta interferons reduces the relapse rate by an average of 30% which is equivalent, on average, to one avoided relapse every two and a half years. It has also been shown that interferon beta reduces the frequency and severity of exacerbations as well as increases exacerbation-free periods in the short term.

- **Interferon beta -1b *(Betaferon®)***

Betaferon® (also known as Betaseron®) was the first disease-modifying drug introduced for MS, and is a well-established treatment around the world (Schering AG, 2006:2). According to Schering AG (2006:2). Betaferon® has a broader background of experience than any other MS medication. Betaferon® has been approved for all relapsing forms of MS in the US, Europe, Japan and also in South Africa, and is the only multiple sclerosis treatment that has been available to patients for almost 20 years (Bayer Healthcare Pharmaceuticals, 2009).

× *Pharmacological classification*

As for interferon beta-1a *(refer to page 87).*

× *Mechanism of action*

As for interferon beta-1a *(refer to page 87).*

× *Dosage and administration*

Adult dose: 0.25 mg subcutaneously every other day (Schering (Pty) Ltd, 2005).

Administration in children: According to Snyman (2010:349), interferon beta is contraindicated in children younger than 16 years of age.

× *Outcome*

Betaferon is the longest studied multiple sclerosis treatment with over 20 years of clinical and safety data (Bayer Healthcare Pharmaceuticals, 2009). It is indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Interferon beta-1b is shown to delay the progression to clinically definite MS (CDMS) when used from the first clinical sign of MS (Bayer Healthcare Pharmaceuticals, 2009). It is also has the ability to reduce the number of MS episodes by one third, and the frequency of moderate to severe episodes by as much as 50 per cent (Schering AG, 2006:1).

Results from the BENEFIT (Betaferon® in Newly Emerging Multiple Sclerosis for Initial Treatment) clinical trial showed that Betaferon® 250 mcg reduces the risk of developing clinically definite multiple sclerosis (MS) by 50% compared with placebo. Furthermore, patients receiving Betaferon® were doubly better protected against developing MS, as defined by the McDonald Diagnostic Criteria (Schering AG, 2006:1).

Sixteen years' follow-up of people treated with Betaferon® has shown that it is not only effective in treating MS, but also safe and well tolerated (Schering AG, 2006:2).

2.8 Adverse reactions, contra-indications and drug-drug interactions of biologic immunomodulators

2.8.1 Introduction

Any medical intervention, as well as watchful waiting or observation, carries inherent risks. This concept is the fundamental basis by which physicians provide patient care. Relative risks and benefits are weighed for each therapy. It therefore is required of the prescribing physician to obtain a working knowledge of the benefits and risks of interventions under consideration (Kong *et al*., 2006).

2.8.2 Adverse reactions

Adverse reactions can be broadly classified as predictable or unpredictable in nature. Predictable adverse reactions include over-dosage (a known but undesirable drug effect that manifests because of excessive dosing; side-effects (undesirable physiological effects of a drug); secondary effects (collateral events that occur indirectly as a consequence of the medication prescribed), and drug-drug interactions (interactions between two or more different drugs). Unpredictable adverse reactions include intolerance, idiosyncratic, allergic and pseudoallergic reactions (Kong *et al*., 2006).

Biological medicines, like any other therapeutics, carry potential risks of adverse events. Over time, a number of case studies and randomised trials have demonstrated the potential toxicities with the use of biological response modifiers (Kong *et al*., 2006). A discussion of a few of the most commonly used biologics in autoimmune disorders and their respective potential and reported adverse reactions will give some insight into the safety of these agents.

Table 2.18 lists the most common adverse reactions associated with the biological agents discussed in section 2.2.4. Various resources have been referenced to ensure a complete and comprehensive side-effect profile of each drug.

Table 2.18 Adverse reactions of relevant biologic immunomodulators

Biologic	Common adverse reactions	Serious adverse reactions
TNF-α antagonists		
Etanercept	• Injection site reactions[1,7,8,9,10,11,12] *(within 1-2 hours of infusion, particularly with the first or second dose)* • Upper respiratory infections[1,10,12] • Headache[1,12] • Abdominal pain[12] • Dyspepsia[12] • Asthenia[12] • Nausea, vomiting, diarrhoea[12] • Dizziness[12] • Back pain[12] • Development of antibodies to etanercept[12]	• Risk of infection[1,7,8,9,10,11,12] *(TNF-α inhibitors suppress the immune system and lowers its ability to fight infections. Infections include TB and other infections caused by viruses, fungi or bacteria)* • Risk of cancer[1,7,9,10,12] *(Lymphomas and leukemia, most prevalent in children younger than 18)* • Nervous system problems[1,7,8,9,10,12] *(Including multiple sclerosis)* • Hepatitis B infection[1,8,12] *(In patient with a latent infection)* • Blood dyscrasias[1,8,12] *(Leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia)* • Heart failure[1,7,8,11,12] • Liver failure and jaundice[12] • Psoriasis[1,11] *(New or worsening of existing psoriasis)* • Allergic reactions[1,8,11,12] • Autoimmune reactions[1,7,8,9,10,11,12] *(Including Lupus-like syndrome)*
Infliximab	• Respiratory infections[2,10,12] • Injection site reactions[2,7,8,9,10,11,12] • Headache[2,12] • Rash[2,11,12] • Coughing & soar throat[2] • Abdominal pain[12] • Nausea, vomiting, diarrhoea[12] • Dizziness[12] • Back pain[12] • Development of antibodies to infliximab[12]	• Serious infections[2,7,8,11,12] *(Including TB)* • Risk of cancer[2,7,9,10,12] • Heart failure[2,7,8,11,12] • Interstitial lung diseases[12] • Liver injury[2,8,12] • Jaundice[2,12] • Hepatitis B[12] • Blood dyscrasias[2,8,12] • Nervous system problems[2,7,8,9,10,11,12] • Allergic reactions[2,8,11,12] • Autoimmune reactions[2,7,8,9,10,11,12] *(Including Lupus-like syndrome and psoriasis)*
Adalimumab	• Injection site reaction[3,7,8,9,10,11,12] • Upper respiratory infections[3,10,12] • Headaches[3,12] • Rash[3,11,12] • Nausea, vomiting, diarrhoea[3,12] • Dizziness, back pain[12] • Hypertension, paraesthesias[12]	• Serious infections[3,7,8,9,10,11,12] *(Including TB)* • Allergic reactions[3,8,11,12] • Hepatitis B infection[3,8,9,12] *(In patients with latent infection)* • Nervous system problems[3,7,8,9,10,11,12] • Blood problems[3,8,12]

Table 2.18 Adverse reactions of relevant biologic immunomodulators *(continued)*

	• Increased alkaline phosphate levels[12]	• Heart failure[3,7,8,11,12] • *(New or worsening of existing failure)* • Autoimmune reactions[3,7,8,9,10,11,12] *(Including Lupus-like syndrome and psoriasis)*
Anti-CD20 agent		
Rituximab	• Cytokine relapse syndrome[12] • Fever[4,12] • Infection, rashes[4,12] • Urticaria, pruritis[12] • Headache[4,12] • Pain • Nausea[4] • Lymphopenia[4,12] • Dysphnoea, bronchospasm, angiodema[12] • Transient hypotension, hypertension[12] • Rhinitis, asthonia[12]	• Fatal reactions within 24 hours of first injection[4,8,10,12] *(Hypoxia, acute respiratory distress syndrome, pulmonary infiltrates, myocardial infarction, ventricular fibrillation and cardiogenic shock)* • Tumor lysis syndrome[4,8,12] *(Acute renal failure)* • Severe mucocutaneous reactions[4,8,10,12] *(Including Stevens-Johnson syndrome)* • Hypersensitivity reactions[4,12] • Cardiac arrhythmias & angina[4,12] • Progressive multifocal leukoencephalopathy[12] • Hepatitis B[8,12] *(Flare ups in patients with latent infection)*
Beta interferons		
INF-β 1-a	• Injection site disorders[5,11] • Influenza-like symptoms[5,11] *(Including headache, fatigue, fever, rigors, chest pain, back pain, myalgia)* • Abdominal pain[5] • Elevation of liver enzymes[5] • Hematologic abnormalities[5,11]	• Depression[5] *(May lead to suicidal tendencies)* • Risk to pregnancy[5] • Allergic reactions[5,11] *(Including respiratory depression and anaphylaxis)* • Injections site problems[5,11] *(May cause necrosis at injection site)*
INF-β 1-b	• Lymphopenia[6,11] • Injection-site reactions[6,11] • Asthenia[6,11] • Flu-like symptom complex[6,11] *(Including headache, pain, hypertonia, myasthenia)*	• Depression[6,11] • Risk to pregnancy[6] • Allergic reactions[6,11] *(Respiratory depression and anaphylaxis)* • Injections site problems[6,11] *(May cause necrosis at injection site)*

[1]Immunex corporation, 2009; [2]Centocor Ortho Biotech Inc., 2009; [3]Abbott laboratories, 2009; [4]Biogen Idec Inc., 2003; [5]Serono, Inc., 2003; [6]Schering (Pty) Ltd, 2005; [7]Kong *et al*., 2006:477-479; [8]Callen, 2007:10-11; [9]Fleischmann & Yocum, 2004:S14-S17; [10]Lee & Kavanaugh, 2005:902-903; [11]Pichler, 2006:917; [12]Sweetman, 2010.

2.8.3 Contra-indications and interactions

Martin (2003:108) defines a contra-indication as *"any factor in a patient's condition that makes it unwise to pursue a certain line of treatment"*.

The concept of drug-drug interactions is made clear by Gonzalez and Tukey (2006) when they describe it as the phenomenon where two drugs influence each other's metabolism when they are administered simultaneously. When the two drugs are metabolised by the same enzyme, the rate of one or both of their metabolisms are altered, which may cause either an unwanted increase or decrease in the plasma concentration of the drugs, which in turn increases the risk of toxicity or disease relapse.

Table 2.19 (Snyman, 2010:81,200,344,348; Sweetman, 2010; Turner, 2006:378) summarises the most important contra-indications and interactions of the biologics discussed in section 2.2.4.

Table 2.19 Contra-indications and interactions of relevant biologic immunotherapeutics

Biologic	Contraindications	Drug-drug interactions
TNF-α antagonists		
Infliximab	• Severe infections[1,2,3] *(Including abscesses and opportunistic infections)* • Active tuberculosis[1,2,3] • Chronic infections or underlying conditions that may predispose to infections[1,2] • Hepatitis B[1,2] • Moderate to severe heart failure[1,3] • Safety in pregnancy and lactation not established[2,3] • Safety not established in children under the age of 17 – use with caution[3]	• Live vaccines[1,3] • Anakinra[1,3] • Abatacept[1] • Concomitant use with other TNF-α inhibitors[1,3] *(May increase risk of serious infections and neutropenia. Combinations are not recommended)*
Etanercept	• As for infliximab • Children younger that 4 years[1,3] • Wegener's granulomatosis[1,3] • Use with caution in patients with heart failure[1,3] • Use with caution in patients with a history of hepatic abnormalities[2]	• As for infliximab • Sulfasalazine[1] • Combination with other TNF-α inhibitors in Wegener's granulomatosis[1] *(Increases incidence of malignancy)*
Adalimumab	• As for infliximab • Moderate to severe cardiac failure[1,3] • Tuberculosis[1,3]	• As for infliximab • Methotrexate[1] *(May reduce clearance of adalimumab by up to 44%)*
Anti-CD20 agent		
Rituximab	• Extensive tumors[1] • Pulmonary tumor infiltration[1]	• Statins[1] • Cariotoxic chemotherapy[1]

Table 2.19 Contra-indications and interactions of relevant biologic immunotherapeutics *(continued)*

	• Pulmonary insufficiency[1] • Progressive multifocal leukoencephalopathy[1] (PML) • Hepatitis B[1] • Cardiovascular disease[1]	
Beta interferons		
INF-β 1-a	• Depression or psychiatric disorders[1,3] • Epilepsy or other CNS diseases[1,3] • Severe renal or hepatic impairment[1,3] • Chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver[1,3] • Auto-immune hepatitis[1] • Cardiac disorders[1,3] • Myelosuppression[1,3] • Poorly controlled thyroid dysfunction[1] • Pulmonary disease[1] • Diabetes mellitus[1] • Auto-immune diseases[1,3] • Coagulation disorders[1] • Children under the age of 16[1,3] • Pregnancy and lactation[3]	• Inhibits hepatic oxidative metabolism via cytochrome P450 enzymes[1,3] • ACE-inhibitors[1] • Analgesics[1] • Anticoagulants[1] • Antineoplastics[1] • Antivirals[1] • Thalidomiden[1] • Theophylline[1]
INF-β 1-b	• *As for interferon beta 1-a*	• *As for interferon beta-1a*
[1]Sweetman, 2010; [2]Turner, 2006:378; [3]Snyman, 2010: 81,200,344,348,349.		

2.9 Cost impact of biologics

2.9.1 Introduction

Biologic medicines are indicated to treat conditions for which few other alternative treatment options are available, but at costs that can be considerably higher than those of traditional medicine. According to Cohen *et al.* (2006:S25), most biologics fall into the category of "specialty pharmaceuticals", which are defined as "*premium-priced infused or injected medicines that require special handling, and are indicated for long-term and/or life-threatening diseases*".

The total population of specialty pharmaceutical users is relatively small, because not many people are afflicted with the conditions currently treated with specialty medicines. However, specialty pharmaceutical spending is quickly increasing as more indications are found for existing biologics and new biologics enter the market to treat more common diseases (Joyce *et al*., 2008:821).

Cohen *et al.* (2006:S24) reported that in 2006, the biological medicine market was already growing at an extraordinary tempo, being the fastest growing sector of the pharmaceutical marketplace. Cohen *et al*. (2006:S25) furthermore stated that from a managed care perspective, various contributing factors drive the fast growth of biologics. A few key contributors, among various other economic factors, include increased

- availability of biologic targets;
- utilisation and additional indications of approved drugs; and
- approval of biologics for more common conditions.

This section focuses on the economic growth of biologics during the last decade. [RSA Rand (R)/$US = 6.38112 (2005); 6.78812 (2006); 7.06926 (2007) and 8.27505 (2008)] (OANDA Corporation, 2010).

2.9.2 Global and regional cost impact of biologics

IMS (Information Management System) Incorporated, a global pharmaceutical and health care information company, posted various top-line industry data on global and US pharmaceutical sales for the period 2001 to 2008 (IMS Inc., 2009). Figure 2.16 illustrates global pharmaceutical sales between 2001 and 2008. Sales are presented in US dollars in Figure 2.16.

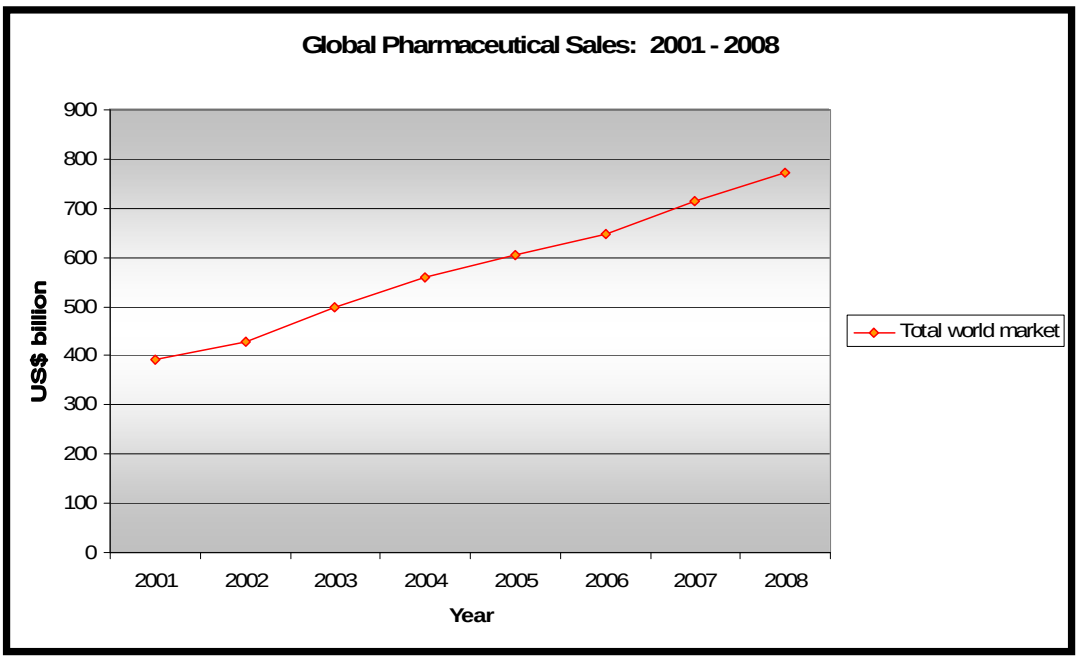

Figure 2.16 Global pharmaceutical sales: 2001 – 2008 (Compiled from IMS, 2009)

In Figure 2.16 it is evident that sales of pharmaceutical products are increasing annually worldwide, growing from a 600 billion dollar (R3 828.67 billion) market in 2005 to an 800 billion dollar (R6 620.04 billion) market in 2008. That is a 70% growth within 4 years.

To investigate which pharmaceutical products contributed to this dramatic growth, Figure 2.18 indicates the top 15 therapeutic classes by global sales and Figure 2.18 rates the top 15 worldwide pharmaceutical products in 2006 and 2008 (Compiled from IMS Inc., 2009).

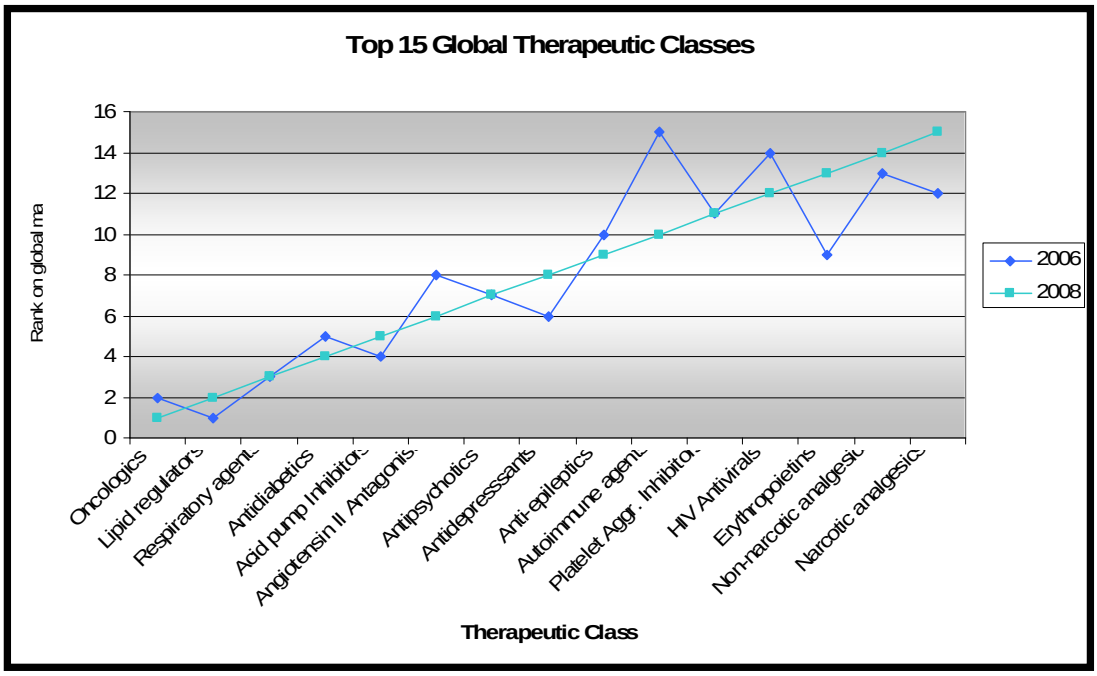

Figure 2.17 Top 15 global therapeutic classes (Compiled from IMS Inc., 2009)

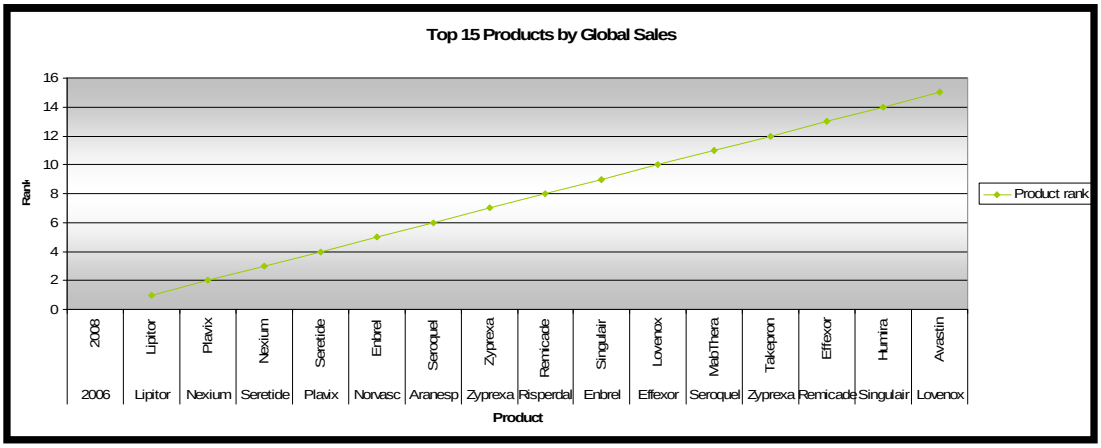

Figure 2.18 Top 15 therapeutic products by global sales (Compiled form IMS Inc., 2009)

Figure 2.17 shows a dramatic increase in global sales of autoimmune agents from 2006 to 2008, moving from position 15 on the worldwide rank in 2006 to position 10 in 2008. Figure 2.18 shows biologic autoimmune agents Enbrel®, MabThera® and Humira® moving up the global ranks from 2006 to 2008. Expenditure on Enbrel® increased from 2006, where it held position 9 on the top 15 products list, placing it in position 5 in 2008. Spending on MabThera® and Humira® also increased from 2006 to 2008. The RA biologics (i.e. Enbrel®, MabThera®, Humira®) ranked positions 11 and 14 respectively in 2008, while neither of these products were among the top 15 global products in 2006.

In the US, anti-arthritics (or biological response modifiers) were ranked 9th on list of the top 15 therapeutic classes by US sales. The increase in expenditure on this class of pharmaceuticals is impressive when considering that it rose from 2.6 billion dollars in 2004 to 6 billion dollars in 2008 (IMS Inc., 2009). The RA biologics Enbrel® and Remicade® (Revellex® in South Africa) reached the 7th and 13th top US pharmaceutical products by sales in 2008 respectively (IMS Inc., 2009).

In South Africa, Mediscor® PBM reported on the expenditure of the top therapeutic groups for their beneficiaries for 2008. Cytostatics were in position 3 in 2008, after moving up from position 4 in 2007, subsequent to antihypertensives and hypolipidaemic agents in positions one and two respectively. It is important to note that even though cytostatics accounted for 5.5% of total medicine expenditure, only 0.7% of total beneficiaries were using the medicines in this therapeutic class, compared to 18.2% and 9.8% of total beneficiaries utilising antihypertensives and hypolipidaemic agents respectively (Bester & Badenhorst, 2009:14).

Mediscor® also reported on the top 50 products that contributed to the total medicine expenditure by their company for 2006 to 2008 (Bester & Badenhorst, 2009:17). The breast cancer drug Herceptin® ranked position nine (9) in 2006, but ranked position three (3) by the end of 2008 (Bester & Badenhorst, 2009:17). Although the utilising beneficiaries only accounted for 0.01% of the total number of beneficiaries, Herceptin® accounted for 0.8% of the total expenditure in 2008. MabThera®, a biologic drug used in the treatment of both cancer and rheumatoid arthritis, moved from position 23 in 2006, to position sixteen (16) in 2007, to ranking fifteenth (15th) in 2008, contributing to 0.5% of total medicine expenditure while only being utilised by 0.02% of total beneficiaries (Bester & Badenhorst, 2009:17). The biological musculoskeletal agent Enbrel®, which is used to treat rheumatoid arthritis, moved up from position 86 in 2006 to rank 42 at the end of 2008 (Bester & Badenhorst, 2009:18). Although Enbrel® is only used by 0.01% of the total number of beneficiaries, it contributed 0.3% to total medical expenditure for 2008 (Bester & Badenhorst, 2009:18).

It is evident that biopharmaceuticals are greatly contributing to escalating health care costs worldwide. From the literature it is also clear that cancer therapies and biologic immunotherapeutic agents are notable cost drivers in global health care expenditure.

According to Vogenberg *et al.* (2004:37), with increases in prescription medicine expenditure expanding beyond health benefit plan cost increases, along with the growing proportion of prescription medicine costs represented by biologics, it is no surprise that the cost impact of biologics is receiving a great deal of attention.

Joyce *et al*. (2006:824) conducted a study on the impact of specialty drugs on the use of other medical services. The objective of their study was to examine whether initiation of a biologic agent to treat two autoimmune disorders – RA and MS – affects the use of other medical services. The results of their study, however, included data on the annual total and out-of-pocket spending for RA and MS patients.

The results of the study conducted by Joyce *et al.* (2006:824) are summarised in this section to serve as an example of the cost impact of two of the autoimmune diseases investigated in this dissertation. The summary only includes results reflecting expenditures associated with the use of biologics in RA and MS, and not the impact of biological therapies on the use other medical services. A brief discussion of the study design will precede the results to facilitate a better grasp thereof.

The ***research question*** asked whether the initiation of a biological agent to treat MS and RA affected the use of other medical services.

The ***study design*** consisted of a longitudinal analysis from 1997 to 2005, during which time administrative, claims, and benefit information was gathered for 453 commercial health plans. The study population was restricted to patients with no less than 2 primary diagnoses for RA or MS. The claims captured all health expenditures that reflected total annual payments made by beneficiaries (co-payments, deductibles and excluded expenditures) by all third party payers (medical aid schemes).

The ***study sample*** included 30,761 RA patients and 8961 MS patients who were considered "newly diagnosed" if they had had at least one year of claims data prior to the date of the first biologics claimed. "Initiation of a biologic" was defined on the absence of any previous use thereof in earlier years.

The ***study methods*** consisted of negative binomial models being estimated for the number of doctors' visits, procedures and hospitalisations. The most commonly used procedures used in the treatment of RA and MS were identified and procedures costing 100 dollars (R638.11) or more were selected.

The ***results*** showed that it was relatively expensive to treat patients with RA or MS, regardless of their therapy.

Tables 2.20 and 2.21 (adapted from Joyce *et al.*, 2006:825) show the distribution of total and out-of-pocket health care expenditures for RA and MS patients, by service type.

Table 2.20 Annual distribution of total and out-of-pocket spending for RA patients*

	Total spending ($)			***Out-of-pocket spending ($)***		
Service type	*Mean*	*90th percentile*	*95th percentile*	*Mean*	*90th percentile*	*95th percentile*
Inpatient	5318	15,054	33,811	1672	762	7610
Outpatient	6481	15,290	22,308	1741	3891	7033
Prescription medicine						
Biologics	1757	6887	13,816	109	52	272
Nonbiologics	674	1674	2710	120	285	485
Non-RA medicine	4277	8842	14,516	877	1727	2808
TOTAL	**18,506**	**44,926**	**67,563**	**4518**	**9061**	**18,971**
***Annual spending for 2004-2005**						

Although treatment of these conditions is associated with high costs, the co-payments expected to be made by patients are relatively modest when taking into consideration that mean annual spending for RA patients surpasses 18,000 dollars (R114 860.16), and mean out-of-pocket expenditure for RA patients is 4,500 dollars (R28 715.04) per annum (Joyce *et al.,* 2006:824). Despite the fact that all of the patients included in the study population were privately insured through large third party payers, some patients did, however, incur higher costs. For example, 10% of RA patients incurred costs of 45,000 dollars (R287 150.40) or more per year, with out-of-pocket expenditures exceeding 9,000 dollars (R57 430.08) annually, and 5% of patients had an annual out-of-pocket expenditure of 19,000 dollars (R121 241.28) and more (Joyce *et al*., 2006:824).

Table 2.21 Annual distribution of total and out-of-pocket spending for MS patients*

	Total spending ($)			***Out-of-pocket spending ($)***		
Service type	*Mean*	*90th percentile*	*95th percentile*	*Mean*	*90th percentile*	*95th percentile*
Inpatient	3261	3861	15,891	1069	157	1366
Outpatient	4311	10,970	16,357	1187	2475	4506
Prescription medicine						
Biologics	3546	13,773	17,100	125	233	432
Nonbiologics	202	32	155	48	10	36
Non-MS medicine	2958	7022	10,668	644	1322	2100
TOTAL	**14,278**	**33,482**	**48,704**	**3073**	**4859**	**9250**
***Annual spending in 2004-2005**						

Annual expenditure for MS patients was 14,278 dollars (R91 109.63) on average with a mean out-of-pocket spending of about 3,000 dollars (R19 143.36) per year. Only 5% of MS patients incurred costs higher than 9,250 dollars (R59 025.36) per annum (Joyce *et al*., 2006:824). Figure 2.19 and Figure 2.20 graphically illustrate the distribution of total spending for RA (Figure 2.19) and MS (Figure 2.20) patients before and after starting to treat each condition with the appropriate biological agents.

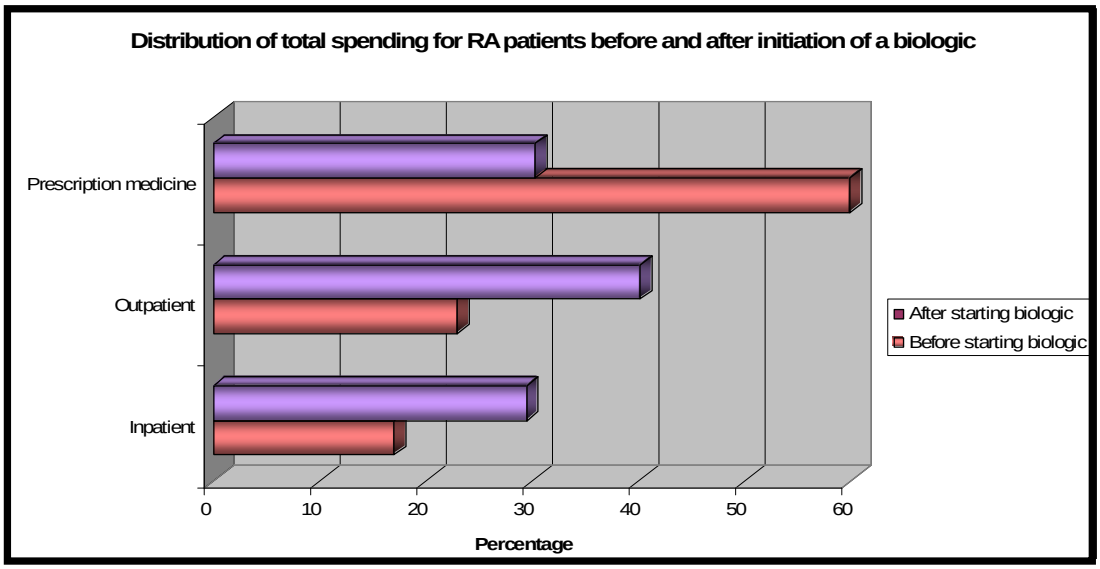

Figure 2.19 Distribution of total spending on RA before and after initiation of a biologic (Compiled from Joyce *et al.*, 2006:825)

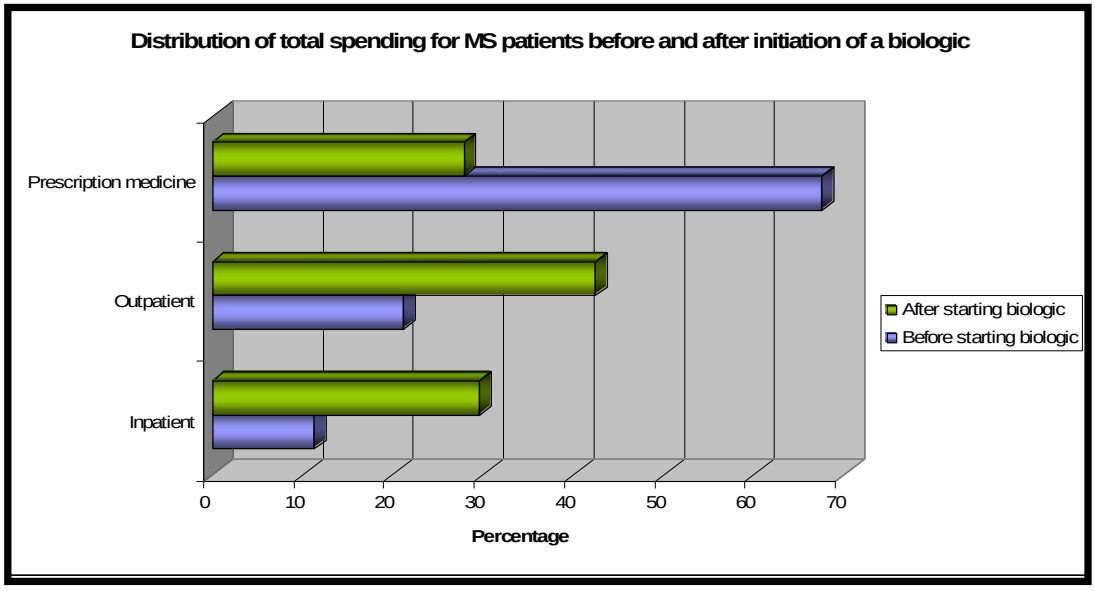

Figure 2.20 Distribution of total spending on MS before and after initiation of a biologic (Compiled from Joyce *et al.*, 2006:825)

Figures 2.19 and 2.20 indicate that the distribution of health care spending shifted after treatment with a biological agent had been initiated. Spending on pharmaceuticals rose to between 60% and 70% of total health care spending in the post initiation years from being a mere 20% to 30% of total health care expenditure in the pre-initiation years. As the biologics market is growing at twice the rate of traditional pharmaceutical medicine, significant cost pressures are placed on employers, insurers and patients (Petigara & Anderson, 2008:1).

Thus, even though according to Joyce *et al.* (2006:827), biologics may reduce other types of service use, the savings do not come close to counterbalancing the full cost of these drugs, since a full regimen of biologic therapies for these conditions can easily cost 15,000 dollars (R95 716.80). As a result, serious concerns have been raised about the value of biologics – not only because of the costs associated with making these drugs available to patients and the high costs brought upon patients themselves, but also about the efficacy of these drugs (Goff *et al*., 2008:14).

According to Krouse (2008) the emergent field of high cost biologic medicines, as well as the several hundred prospective therapies currently being researched, have caused even medical aid schemes to realise the growing importance of biologics, and medical schemes are adapting their insurance policies accordingly.

Goff *et al.* (2008:11) describe health insurance as a tool that distributes the consequences of predictable-but-rare, high-cost events. They add however, that the primary purpose of medical insurance would be contradicted by the results of attempting to restrict utilisation of biologics at the expense of patients who would benefit from them. Goff *et al*. (2008:11) are therefore of the opinion that health insurers should make biologics available to patients who will probably benefit from them – without resorting to high cost sharing – on the condition that they are utilised sensibly, add value to health care, facilitate better productivity and benefit society in general.

Silverman (2005:36) states that the challenge managed care organisations (MCOs) are faced with in their attempts to make high-cost biologics available to patients lie in answering various difficult questions, without committing ethical lapses: Should MCOs cover high-priced biologic treatments? Can they afford to cover them? Can they afford not to cover them? How will such decisions be made? According to Silverman (2005:36), in their search for answers to these questions, third-party payers will not only have to analyse their strategies for coverage, but also respect what is in the patient's best interest.

Joyce *et al*. (2006:821) agree that public and private payers' primary challenge is balancing patients' access to biologics with the need to restrict health care expenditures; and according to Carapinha (2008) the same sentiment applies to biologics in South Africa – although they are clinically effective, they are also relatively expensive. Since in South Africa biologics are primarily used by patients in the private health care sector, the researcher thought it relevant to review a number of South African health care statistics:

Behrman (2009:1) disclosed the following statistics on the South African health system in 2009:

- Health care is responsible for 8.5% of the Gross National Product of RSA. Of this 8.5% of GDP, 5% of all health expenditure is spent on 14% of the population, whereas the remaining 3.5% is spent on the other 86% of the population.
- The total expenditure on health in 2006 was R117 billion, of which R57 billion was spent in the private sector and R59 billion was spent on the public sector.
- R2 645.00 was spent on every patient in the public sector, compared to R9 349.00 on every patient in the private sector.

From these statistics, it is evident that health care expenditure on the private health care sector is far greater than expenditure in the public health care sector. According to McIntyre and Thiede (2007:38), even though the private health care sector accounts for less that 15% of the total population of South Africa, expenditure in this sector is continuing to increase at rates far exceeding the South African inflation rate. This could be attributed to the fact that medical schemes, that form a component of the private health care sector, are the largest financing intermediaries in South Africa, accounting for nearly 46% of total health care expenditure, and also the primary financers of biologics (McIntyre & Thiede, 2007:38).

Carapinha (2008:62) states that access to biological medicines is contested terrain between the manufacturers of biological medicine and the payers (medical schemes) – often to the disadvantage of patients. Carapinha argues that biologics, and other clinically effective, high-priced medicines can be introduced into the health care market by means of cost-sharing agreements, a tool through which manufacturers and payers can manage the risk of such an introduction.

According to Goff *et al*. (2008:29), cost sharing and prior authorisation are the most customary techniques to control access to biologics, but several other tools for restricting access also exist. The same tools that have been employed to manage conventional drugs

in the past are also used for biologics and other specialty pharmaceuticals. These include (Goff *et al*., 2008:29) the following:

- Prior authorisation – criteria are determined that must be met prospectively before coverage for a pharmaceutical product will be approved (Goff *et al.*, 2008:29). Robinson (2006:1207) considers the necessity for physicians to provide documentation about a patient's diagnosis and treatment in order to receive authorisation to prescribe biologics, as a step in "step therapy" that permits a patient to receive biologics only after other recommended treatments have proved unsuccessful.

- Formulary management - financial incentive and disincentives are employed to propel utilisation of particular products, while discouraging use of others.

- Utilisation review - validates the medical necessity of a treatment.

- Claims review – a retrospective assessment of whether drugs are used in proper dosages.

- Evidence-based guidelines - a standard of care is established, based on clinical trials or real-world outcomes.

- Case management - parallel to disease management with the exception of involving individualised care programmes for patients who need specialty therapeutics.

The Zitter Group in America researched commercial payer strategies for managing biotechnology medicines over a two-year period (Baker, 2005:45). In their analysis, researchers identified five distinct stages through which payers will move as they search for ways to exert greater control over biotechnology expenditure. According to Baker (2005:45), the vice president for client strategy and analytics of The Zitter Group in San Francisco, novel tools and strategies to reduce total biotechnology costs are introduced into each stage. In each stage the complexity of the strategies increase, and each stage requires better management tools, diagnostics and data than the previous one to reach the desired objectives.

Baker (2005:49) listed the five stages of biotechnology as follows:

- Buy and bill, which offered payers limited control of cost or utilisation, and presented less a management strategy than actually handing over management to providers.

- Specialty pharmacy, self-administration, and reimbursement changes, as based on the principle that payers sign contracts with specialty pharmacy providers to eliminate physician drug mark-up on specialty pharmaceuticals and occasionally negotiate advantageous pricing. The emphasis on self-administration also eliminates spending on physician office visits.

- Category narrowing and preferred products would have the same aim as formulary management.

- Benefit design and cost-sharing innovation, which means that insurers will turn to more inventive benefit designs that will raise patient co-payments and give employers novel coverage options.

- Genomic diagnostics and genetic risk management, which rely on the evidence that one agent is superior to another on molecular or genetic level.

According to Baker (2005:45), The Zitter Group's research suggests that rheumatoid arthritis and multiple sclerosis are two of several categories in which payers have reached the end of stage two, and MCOs will in all probability be making attempts to move on to stage three of the management process. He adds that the growing environment of biological therapies with sizeable price tags will necessitate the development of more sophisticated economic models, as well as a more comprehensive approach to benefit design and cost-sharing.

The cost impact and financial burden of biologics can thus be summed up as follows: even though biologics only account for 1% to 2% of total health expenditure, their emergence has nonetheless introduced a new facet into the cost equation, since one month's treatment can total thousands of rands and a year's expenditure can easily amount to millions (Goff *et al*., 2008:35). Furthermore, spending on biologics increases mostly because additional uses for a small number of existing biopharmaceuticals have been approved, and not because of the introduction of new biological products (Goff *et al*., 2008:35).

Goff *et al.* (2008:36) recommended that purchasers and payers should concentrate their efforts on identifying patients who would benefit from biologics, rather than trying to restrain biologics' use across the board. It is also important for all parties to take into consideration that the price of biologics, even though it appears high, is merely the justifiable price of medical innovation.

Yet payers, insurers and patients are still heavily distressed by the high cost of biologics, which is understandable. However, the concept of follow-on biologics proposes a possible means by which the financial burden of biopharmaceuticals can be lessened. Competition from follow-on biologics could potentially reduce prices of biologics and ease the cost burden of these therapies (Petigara & Anderson, 2008:2).

According to estimates by the US Congressional Budget Office (2007:1), the establishment of regulations for follow-on biologics can reduce total expenditures on biologics by 2 billion dollars (approximately R16 billion) between 2009 and 2013 (US Congressional Budget Office, 2007:1).

2.10 Biosimilars: The follow-on biologics

The terms "biosimilar" or "follow-on biologic" refer to products that are alleged to have properties similar to existing biological products and are biologics marketed after the expiration of patents of original biologics (Genentech, 2009).

Follow-on biologics are not generic medicine. A generic medicine is a product that is shown to be equivalent to an innovative drug with regard to active ingredient, dosage form, strength and effectiveness, and is generally designated as therapeutically interchangeable with the original drug (BIO, 2007). The concept of generics as used for small molecules cannot be applied to biologics (Baumann, 2006:17), and therefore the term "biogeneric" is rarely used, as it can be misleading. The term "biosimilar" is preferred when referring to follow-on biologics.

The complex physico-chemical properties of proteins make it substantially more difficult to confirm bio-equivalence with biologics, especially since identical copies of biologics cannot be made and even a minute deviation from the original drug can potentially lead to undesirable health outcomes. In addition to this, each protein has a unique structural organisation pattern that influences the way it works in the body. So, even if two biologics are chemically the same, they may have differing biological effects due to variations in the structural folding. Furthermore, since the properties of a biologic often depend directly on the nature of the manufacturing process, it is difficult to demonstrate equality of the same biologics if they are produced by differing processes. A follow-on product can therefore only be made similar, but not identical to the original drug (Genentech, 2009).

The FDA and foreign regulators have indicated that on the basis of the elaborate science involved, the generic drug approval pathway is not suitable for complex biologics (BIO, 2007).

According to Frank (2007:841), patents covering current biologics will expire before long, but the FDA does not have a regulatory process for follow-on biologics in place. According to BIO (Biotechnology Industry Organization), a leading advocate to create a pathway for the approval of biosimilars, the lack of an established legal pathway for such approvals to be made by the FDA, is the first and most obvious legal issue of concern in the discussion of whether and how to approve follow-on biologics.

At this point in time, no regulatory pathway for the approval of biosimilars is in place. Manufacturers and international approval authorities are faced with various legal issues which have to be resolved before such a pathway can be developed and biosimilars can reach the global market (BIO, 2007).

Once these issues have been resolved though, a well-constructed pathway for the approval of biosimilars will lower costs through increased competition, expand access to lifesaving medicines, protect patient safety and promote further biomedical innovation.

2.11 Legislation

Biologics are currently not commonly available in South Africa. In fact, until very recently medical aid schemes did not make biologics available to their beneficiaries, including those patients with RA, MS or Crohn's disease. Their high prices may to a certain extent be responsible for this, but since 2005/2006 patients are stepping up their campaign to get South African medical schemes to provide them with these drugs (Kahn, 2006:1).

The first question that has to be asked is, however: Are medical aid schemes within their rights to refuse payment of biologics?

Yes. According to Kahn (2006:1), the Council for Medical Schemes' (CMS) stand on this is that medical schemes can choose whether to provide biologics to these patients or not – even though RA, MS and Crohn's disease are included in the list of Prescribed Minimum Benefits (PMBs).

PMBs are a set of designed benefits, to ensure that all medical scheme members have access to certain minimum health services. In terms of the Medical Schemes Act (131/1998), PBMs are included and medical schemes have to cover the costs related to the diagnosis, treatment and care of among others, 27 chronic conditions defined in the Chronic Disease List (CDL) (Council for Medical Schemes, 2005:2). The guidelines set by the CMS state that PMB treatment may never be less than the care and treatment available in the state sector, and the regulations detail what *must* be paid.

The minimum medicines for treatment of all PMB conditions have been published in the Government Gazette (SA, 2003). These treatment algorithms illustrate the standard treatment protocols for each chronic condition; it assures the patient of good quality treatment, and reassures the medical scheme that it will not have to pay for unnecessary treatment (Council for Medical Schemes, 2005:3). A medical scheme may decide for which medicines it will pay for each chronic condition, as long as the treatment is not below the standards published in the treatment algorithms. According to the CMS, the algorithms currently available on the CMS website have been reviewed, but the new regulations have not been implemented yet as the CMS is still in the process of getting the new regulations signed by the minister of health (Council for Medical Schemes, 2009). Therefore, even though RA, MS and Crohn's disease are three of the 27 chronic diseases in the CDL, the current algorithms do not cover biologics, and since the state sector does not provide

biologics (because it is too costly), the PMB regulations do not force medical schemes to fund this (Council for Medical Schemes, 2009).

This leads to a next question: Is advocating the right of access to biologics a lost cause?

No. Any medical scheme must pay for the additional treatment if a patient's physician can prove that the standard medication is ineffective or detrimental to his/her condition (Council for Medical Schemes, 2005:4).

The CMS ruled in 2008 that Discovery Health Medical Aid had to pay for the RA biological agent Enbrel®, after one of their beneficiaries appealed their decision not to pay this drug in full. According to Metzer (2008), *"the ruling from the CMS implied that it is illegal for medical schemes to charge a levy for a biologic when the patient has already tried all the other medicine in that category without success".* Treatment with a biological agent is, however, considered as an absolute last resort. In their guidelines for biological therapy, the South African Rheumatism and Arthritis Association states that patients that are to use biological therapies must be registered with the SARAA Biologics Registry. The guidelines add that the prescribing of biological therapies is restricted to registered rheumatologists and that accreditation for the use of biologics may be sought from SARAA Executive Committee providing the physician can prove sufficient experience in rheumatology and regular attendance of appropriate conferences (SARAA, 2009:1).

2.12 Pharmacoeconomic aspects of biologic immunomodulating medicine

2.12.1 Introduction

New medical interventions continually enter the field of clinical practice. These new interventions, that also include medicine, often provide a slight advantage over existing treatment, but generally at a higher cost. Rascati (2009:2) states that concerns surrounding this cost-benefit relationship are the reason for the increasing interest in the economic impact of clinical care and medical technology.

This escalating interest in the economic implications of health care has evolved into a discipline dedicated to attempts to determine whether the added benefit of a new pharmaceutical intervention is worth the higher cost associated with that intervention. This discipline is called *pharmacoeconomics* (Rascati, 2009:2).

2.12.2 Pharmacoeconomics

Pharmacoeconomics is a relatively new discipline that started in the 1970s (Struwig *et al*., 2009:2). As a research area, pharmacoeconomics is defined as *"the description and analysis of the costs of drug therapy to health care systems and society"* (Townsend, 1987 *as quoted by* Bootman *et al*., 2005:3).

Pharmacoeconomics thus adopts and applies the principles and methodologies of health economics (costs) to the field of pharmaceuticals and pharmaceutical policy (drug therapy) (Walley *et al*., 2004:9). By applying pharmacoeconomic principles, the costs and consequences of pharmaceutical products and services can be identified, measured, and compared (Rascati, 2009:2).

According to Walley *et al*. (2004:9), the principles of pharmacoeconomics are based on a straightforward theoretical concept, i.e. that of cost-effectiveness. This concept is used to imply one of two things: i) that clinicians aspire to achieve a predetermined outcome at the

least possible cost, and ii) that clinicians want to maximise the benefit for a patient generated from a given limited number of resources (Walley *et al*., 2004:9).

Rascati (2009:2) states that because health care costs continue to increase annually, the need to understand how limited resources can be applied most effectively and efficiently has arisen. Pharmacoeconomics satisfies this need by estimating the value of patient outcomes for the expenditure on health care interventions. Through these estimates, the objectives of *improved health outcomes* and *decreased health care costs* are combined. Pharmacoeconomics thus serves as a tool with which decision makers can select the most efficient options from a range of health care options to maximise the health care benefit of the population served (Walley *et al*., 2004:9).

2.12.3 Pharmacoeconomic aspects of biologics

The use of biologics to treat various chronic and life-threatening diseases is a relatively new pharmaceutical intervention. Biologics offer significant advantages over existing therapies, since it offers patients improved quality of life and are also often life saving. Their costs have, however, provoked various questions as to how valuable these treatments really are (Peskin, 2008:1).

According to Peskin (2008:1), assessing the value of a treatment is difficult, because "value" is a subjective measure. Patients, physicians, pharmaceutical companies and medical schemes may all find value in a drug for very different reasons. For a patient, a drug would be valuable if it allows him or her to achieve a higher quality of life, for a physician a drug that makes the patient feel better and improves clinical outcomes might be valuable, whereas medical schemes may find value in a drug that reduces spending in their medicine budget (Goff *et al*., 2008:17). Goff *et al*. (2008:17), state that the best way of calculating the value of a drug is through weighing these biases against the direct and indirect costs of care. The value of biologics should therefore be determined by how their cost is viewed in the context of other factors, such as total cost of care or loss of productivity.

Kavanaugh (2007:930) states that even though decision makers cannot quite agree on the value of biologics, one point on which there is wide agreement is that pharmacoeconomic considerations should be an integral part of the decision to use biologic therapies.

Emery (2004:56) adds that in order for a meaningful pharmacoeconomic analysis to be performed, the outcomes of the intervention have to be related and comparable. It is thus much more beneficial to measure and compare the outcomes of a treatment when it is only applied to one condition or disease (Emery, 2004:56). Since this dissertation includes the new interventions (biologic medicine) for three different diseases, the researcher chose rheumatoid arthritis to apply the concepts of pharmacoeconomics.

2.12.4 Pharmacoeconomics applied to Rheumatoid arthritis

Emery (2004:56) states that the economic impact of RA is disproportional to its prevalence in the community. Only a small portion of the population (1% to 2%) is affected by RA, but it is still a relatively expensive disease to treat.

RA is a progressive chronic disease that causes functional limitation and physical disability as a result of joint destruction. This characteristic of RA is associated with substantial morbidity and accelerated mortality; since structural damage and disability can occur within the first two years of the disease, it is most beneficial to start with early aggressive treatment, since the costs of the disease increases significantly when joint replacement, disability and losses of quality of life are considered (Scott, 2007:97). The consequence of not treating or inadequately treating RA can thus result in great economic burdens to not only the RA patients and their families, but also to society (Kavanaugh, 2007:929).

The introduction of new biological medicine, in particular the TNF-α inhibitors, has allowed clinicians to achieve improved outcomes for their patients, but the acquisition costs of these new therapies, which is much higher than for older RA therapies, has affected their utilisation (Kavanaugh, 2007:929). The costs implications of managing RA have given rise to numerous studies of the economic value of RA interventions that delay or prevent disability and reduce the associated morbidity and mortality (Emery, 2004:2).

Economic evaluations serve as tools for assisting decision making, and aims to identify the extent to which a particular decision or set of decisions meets the goal of promoting efficiency (Pharmac, 2004:2). According to Emery (2004:55), economic evaluations of RA therapies are critically important in influencing decisions regarding the role of costly, but highly effective new therapies.

Decision makers therefore turn to various pharmacoeconomic analyses for guidance to aid them in their decision making (Pharmac, 2004:2).

Within the framework of pharmacoeconomic research, there are four basic types of pharmacoeconomic analyses; cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). All pharmacoeconomic analyses identify, measure, and compare the inputs (costs) and outcomes (results) of pharmaceutical interventions (Bootman *et al*., 2005:2). In each pharmacoeconomic analysis, the costs are always measured in monetary units (dollars, rands), whereas the outcomes are expressed in differing units depending on the analysis being performed (Rascati, 2009:4).

Goff *et al*. (2008:17) gives examples as to how each of these pharmacoeconomic analyses can be applied to biologics used in RA:

- **Cost-minimisation analysis (CMA)**

A CMA is performed when two drugs or interventions have similar outcomes. Since only the costs of each alternative are compared, a CMA is the simplest analysis to perform (Rascati, 2009:4). A CMA is usually performed to assess traditional drugs of which there are many in a class, like the statins. Since the biologics are specifically engineered to target a particular set of cells in the body, their outcomes are not always equal. A CMA is thus not typically performed to evaluate biologics; however this type of analysis does have some limited applications to biologics. For example: a CMA can be performed to compare two TNF-α inhibitors, like etanercept and infliximab to assess which one is less expensive to use in RA (Goff *et al*., 2008:16). A CMA would include considerations such as the route of administration (where subcutaneous administration is preferred to intravenous administration), the dosing requirements and potential for having to increase the dosage over time.

- **Cost-benefit analysis (CBA)**

A CBA is performed to compare the costs of an intervention, with the costs of not intervening (Wonderling *et al*., 2005:221). In a CBA, both the inputs and outcomes are measured in monetary outcomes, permitting one to weigh the financial costs of a course of action against the expected financial benefits. This allows decision makers to assess whether the benefits

obtained from a certain intervention will exceed the costs of implementation (Rascati, 2009:5).

Although it is relatively straight forward to estimate medical costs, it is difficult to estimate indirect costs, and this complicates CBAs. If a CBA were to be applied to RA, the loss of productivity of the patient would have to be quantified, which means that a projection of a person's income would have to be made. To quantify a patient's satisfaction from improved health involves calculating how much a person is willing to pay to improve his/her quality of life or prevent death, which is a science that hinges on emotional matters rather than facts (Goff *et al*., 2008:18).

- **Cost-effectiveness analysis (CEA)**

A CEA is performed to compare the costs and effectiveness of two interventions that do not produce similar outcomes, i.e. a CEA compares the alternative therapies for the same disease or indication (Walley *et al.*, 2004:13). In a CEA, the inputs are measured in monetary units, and the outcomes (health benefits) are measured in natural units (e.g. years of life saved, epileptic seizures prevented, etc.). A CEA is thus performed to compare interventions whose costs are measured in monetary units, and outcomes are measured in the same natural units (Walley, 2004:13).

Cramer and Spilker (1998:238) explain that a CEA is only capable of indicating relative superiority in answer to questions like "Which is better?" or "What is the cost of obtaining a certain effect?" For example, a CEA can be performed to compare the outcomes of a TNF-α inhibitor with a regimen of methotrexate for RA. Both therapies' outcomes are measured in natural units (years of functional disability prevented or loss of productivity prevented), but the TNF-α inhibitor is expected to yield greater benefits than a regimen of methotrexate. A CEA comparing these two therapies might also take into consideration the extra costs associated with periodic monitoring of liver function with methotrexate because of its toxicity, and additional treatments that may be necessary with biologics or methotrexate (Goff *et al*., 2008:19).

- **Cost-utility analysis (CUA)**

A CUA is used to measure the quality of the number of life years that is gained because of an intervention. CUA is similar to CEA in that the costs are measured in monetary units, and the outcomes are measured in a natural unit.

A CUA does not only measure the years of life saved because of treatment, but takes into account the quality of those years (Rascati, 2009:5). The outcome of interest in a CUA is thus a unit of "quality" or "utility" known as "quality-adjusted life years" (QALY). This is, however, difficult to measure in practice, because quality of life is subjective and differs from patient to patient. QALY would indicate more of a rough estimate than a precise measure, which makes this unit invaluable for most decision makers (Walley *et al*., 2004:115). A CUA can be applied to biologic RA drugs in the same way as a CEA, but the outcomes would be measured based on years of life that are altered by "utility" weights, which range from 1.0 for "perfect health" to 0.00 for "dead" (Rascati, 2009:5).

Establishment of economic benefit in economic evaluations requires rigorous analysis of both the total costs and the consequences of a given therapy (Emery, 2004:2). Studies that consider both the costs and outcomes of treatment include cost-benefit analyses, cost-effectiveness analyses and cost-utility analyses, of which cost-effectiveness and cost-utility analyses are most commonly used in economic evaluations of treatments for RA (Emery, 2004:57).

2.13 Chapter summary

In this chapter the biology of the immune system and its key responses and components involved in autoimmune diseases were discussed to illustrate the place of biologic immunomodulators in the treatment of three autoimmune diseases: rheumatoid arthritis, Crohn's disease and multiple sclerosis. This was followed by an overview of the prevalence, indications and clinical effects of biologics, together with their cost impact on medicine expenditure and the pharmacoeconomic aspects associated with it.

From chapter two it is evident that the development of biologics is still a young branch of the medical and pharmaceutical field, and further research on these substances will be necessary to fully experience their potential. Boehncke & Radeke, 2007:1 agree that only by continually expanding the knowledge about disease driving molecules and the pathomechanisms involved, will science be able to extend the field of biological therapy. Chapter two indicates that the application of biologics has in itself already unravelled new insights into disease processes, and that biologics are already widely recognised as milestones in the history of pharmacology.

Chapter two furthermore reveals that the cost impact and financial burden of biologics have also been recognised by researchers and decision makers alike, though not as a milestone, but as a factor of concern. Even though biologics account for only a relatively small percentage of total health expenditure, their emergence has nonetheless introduced a new facet into the cost equation, since one month's treatment can total thousands of rands and a year's expenditure can easily amount to millions.

Chapter three contains information with regard to the empirical investigation and methodology used to investigate the prevalence and cost of biologic immunomodulators. The following chapter will thus include discussions on the research objectives, research design and methodology as well as the data sources and analyses.

CHAPTER 3

Methodology and Empirical investigation

Chapter three refers to the empirical research methodology. It also includes discussions on the procedures that were followed in obtaining the applicable information, as well as the data analysis that follows. The empirical research includes the statement of general and specific research objectives, the selection and construction of the data source and study population, the outlay of the research design, the selection of measurements and the data analysis. The chapter concludes with an assessment of the reliability and validity of descriptive measures, discussion of the results of the empirical investigation and a conclusion and recommendations.

3.1 Research objectives

The research objectives were stipulated in chapter one and can be further divided into general and specific research objectives.

3.1.1 General research objective

The general objective of this research project was to investigate the prescribing patterns of biological medicines in the treatment of certain autoimmune diseases, and the costs associated with it, in a section of the private health care sector of South Africa.

The research data were obtained by reviewing the patient and prescription information of a medicine claims database for the period 2005 to 2008.

3.1.2 Specific research objectives

The specific objectives of this study were based on the two phases of the study, namely a literature review and an empirical investigation. The literature review has been discussed in chapter two, and the empirical investigation will follow in chapter four. Based on the research questions stated in chapter one, the following specific research objectives needed to be achieved from the empirical phase:

With regard to biologic immunomodulators in general:

- Analyse the current prescribing patterns and cost trends of biologic immunomodulators in a section of the private health care sector of South Africa by using a medicine claims database for the period 2005 to 2008.
- Analyse how biologic immunomodulators influence medicine expenditure of medical aid schemes in a section of the private health care sector of South Africa over time.

With regard to biologic immunomodulators specifically used in the treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease:

- Determine the prescribing patterns of biologic immunomodulators in the treatment of rheumatoid arthritis, multiple sclerosis or Crohn's disease.
- Determine the cost of biologic immunomodulators and how it compares with the cost of other medication (excluding biologics) received by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease.
- Investigate the influence of biologic immunomodulators on the prescribing patterns of other medication (excluding biologics) after treatment with biologics in patients with rheumatoid arthritis, multiple sclerosis and Crohn's disease.

3.2 Research design

Since the general objective of this research project was to establish the usage and costs of biologic immunomodulating medicine in a section of the private health care sector of South Africa, a research design that could accomplish this goal had been selected. The most appropriate research design that could be employed to determine prescribing and utilisation patterns was a drug utilisation review (DUR). This section will explain what a DUR is and what this type of research entails.

3.2.1 Drug utilisation review

In today's health care system the importance of harmonising the quality of care with the cost thereof is continually being underlined (Peterson *et al*., 2007:215). The proper use of medicine is fundamental to accomplish this harmony, and health professionals can assess how medicine is used through a process called *drug utilisation review*.

In 1977, the World Health Organization (WHO) defined drug utilisation research (DUR) as *"the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences"*.

A drug utilisation review is also described as "*a systematic program where data on medicine use is reviewed and measured up to specific, impending standards and corrective approaches are initiated where needed to realise a preferred outcome"* (Perez, 2001). According to Perez (2001), the primary aims of DUR are thus to improve the quality of health care, protect resources that fund medicine, manage individual spending and preserve the integrity of health programmes.

Gama (2008:69) concurs with Perez (2001) and states that drug utilisation studies are employed to assess aspects of the prescribing, dispensing, administering and taking of medication; which would include present and future drug utilisation trends, medicine spending, suitability of prescriptions and estimating prevalence of disease.

Sjöqvist and Birkett (2003:78) are in agreement with Gama (2008:69), but elaborate further by stating that the primary purpose of DUR should first and foremost be to ensure that medicine is appropriately used in populations. They added that it is difficult to comment on rational drug use and prescribing patterns without knowing how the drugs are being prescribed and used. Although DUR may not supply decision makers with all the answers, it may, however, offer insight into some aspects of drug use and prescribing, including patterns, quality, determinants and outcomes of use (Sjöqvist & Birkett, 2003:78). Furthermore, DUR can reflect on the efficiency of medicine usage and therefore aid in setting priorities for the rational allocation of health care budgets.

In the last two decades DUR has grown to be one of the most pressing needs in establishing drug policy (Gama, 2008:69). DUR plays a vital role in the identification of problems that necessitate regulatory and enlightening actions. Drug utilisation studies thus offer the potential for better communication between medicine users and policy makers (Folb, 1989).

Drug utilisation reviews can be performed in three different ways to assess medicine use:

- ***Prospective reviews*** occur before the patient has received the medication. Prospective studies thus assess medicine therapy before the medicine has been administered to the patient.

- ***Concurrent reviews*** are conducted while the patient is receiving the medication. A concurrent study offers the opportunity to intervene and alter a patient's medicine therapy during the time he/she is receiving the medication, when necessary.

- ***Retrospective reviews*** are conducted after the patient has received and used the medication. Retrospective studies review medicine therapy that has already been used by the patient for appropriateness, by making use of data that reflect a patient's medicine history (Peterson *et al*., 2007:218).

The data used in this study consisted of medicine claims from the medicine claims database of a South African pharmacy benefit management company for the period 2005 to 2008. Seeing that this research project was conducted on prescriptions already filled, this study qualifies as a retrospective drug utilisation review.

A brief discussion of a retrospective drug utilisation review will follow as to give a more comprehensive understanding of the scope of this type of research design.

3.2.1.1 Retrospective drug utilisation review (rDUR)

Perez (2001) defines retrospective DUR as *"a systematic process that involves selection, review, analysis, and interpretation of drug use data that are collected and analysed after events occur".*

Arnold and Balu (2010:59) state that, except for their obvious application in pharmacoeconomic analyses, data collected from retrospective databases can also be applied in outcomes research (e.g. analysis of health care practice patterns, epidemiologic analysis of disease progression, prevalence and characteristics of patient populations), evaluation of populations for prediction of future events, for formulary evaluation and to supplement prospective datasets.

A retrospective DUR evaluates medicine therapy after the patient has already received it and therefore has a limited ability to exercise immediately impact on patient care. Retrospective DUR does, however, have the ability to help to identify patterns of drug utilisation that call for extra education of prescribers and patients, and also bring those areas to light where the system is being misused and exploited (Perez, 2001; Peterson *et al*., 2007:218).

The Academy of Managed Care Pharmacy (2009) explains that repetition of unsuitable medication use or abuse can be prevented by implementing prospective standards and target interventions, based on current medication use trends. Thus, the care patients receive from their prescribers may be improved when prescribers have access to and positively act upon the results of retrospective DUR conducted on their patients.

Peterson *et al.* (2007:218) identified various derivates of medicine use that are generally identified by using retrospective DUR:

- Abuse/misuse.
- Appropriate generic use.
- Drug-drug interactions and drug-disease contraindications.
- Inappropriate duration of treatment and incorrect dosage.
- Under-and over-utilisation.
- Therapeutic appropriateness and duplication.

Careful consideration was given to some of the above-mentioned aspects of medicine usage when the retrospective drug utilisation review was conducted and presented in chapter four. The rDUR aimed to identify and evaluate various aspects of the prescribing of biologic immunomodulators in a section of the South African private health care sector, including prescribing patterns and medication costs.

3.3 Research methodology

In this section the methods used in obtaining the relevant data for this research project are discussed, i.e. data source and the selection of the study population.

3.3.1 Data source

For the empirical phase, a retrospective drug utilisation study was done on medicine claims data provided by a Pharmacy Benefit Management (PBM) company database. Data were provided from the PBM's medicine claims database for a four-year period stretching from 1 January 2005 to 31 December 2008.

3.3.2 Study population

A target population was first selected from the total database. All the prescriptions on the database between 1 January 2005 and 31 December 2008 were screened, and each prescription consisting of any medicine item(s) containing one of the following active ingredients was selected:

- Adalimumab,
- Etanercept,
- Infliximab,

- Interferon beta-1a,
- Interferon beta-1b, and
- Rituximab.

The patient pool obtained from the selected prescriptions formed the target population. The patients included in the target population were then identified for RA, MS or Crohn's disease, by applying three "diagnostic codes" to each patient: the ICD-10 MPA code, the ICD-10 claim code and the diagnostic code. The ICD-10 MPA code is the detailed ICD-10 code based on the pre-authorisation by the PBM or the medical aid scheme. The ICD-10 MPA code is the ICD-10 code as indicated by the prescriber or the pharmacy, whereas the diagnosed code is the overall code diagnostic code based on the pre-authorisation by the PBM or the medical aid scheme. Patients were positively identified when at least two of the three relevant codes were assigned to them at least once during the four year study period. Patients who were positively identified for one of the diseases were then grouped together according to their "diagnosis". The three patient groups (RA, MS and Crohn's disease) combined, formed the study population.

A step-by-step diagrammatic illustration of this selection method is given in Figure 3.1. Obtaining the study population through this method of selection ensured that no relevant prescriptions were potentially excluded from the study. The number of prescriptions, patients, and medicine items given in this illustration is for the total four-year period. The total number of prescriptions that contained biological medicines as a portion of the total number of prescriptions on the database for each of the four years is shown in Table 3.1.

Table 3.1 Prescriptions for biologic immunomodulators as a portion of the total prescriptions

		2005	%	2006	%	2007	%	2008	%
Total database	Prescriptions	8,391,836	100	8,906,348	100	7,911,096	100	6,775,873	100
	Patients	1,509,621	100	1,558,090	100	1,178,596	100	974,497	100
	Medicine items	19,500,774	100	21,113,422	100	19,075,724	100	16,439,253	100
Biologic immunomodulators	Prescriptions	1,319	0.016	2,054	0.023	2,971	0.038	3,193	0.047
	Patients	198	0.013	279	0.018	372	0.032	416	0.043
	Medicine items	1,759	0.009	2,829	0.013	3,595	0.019	3,731	0.023

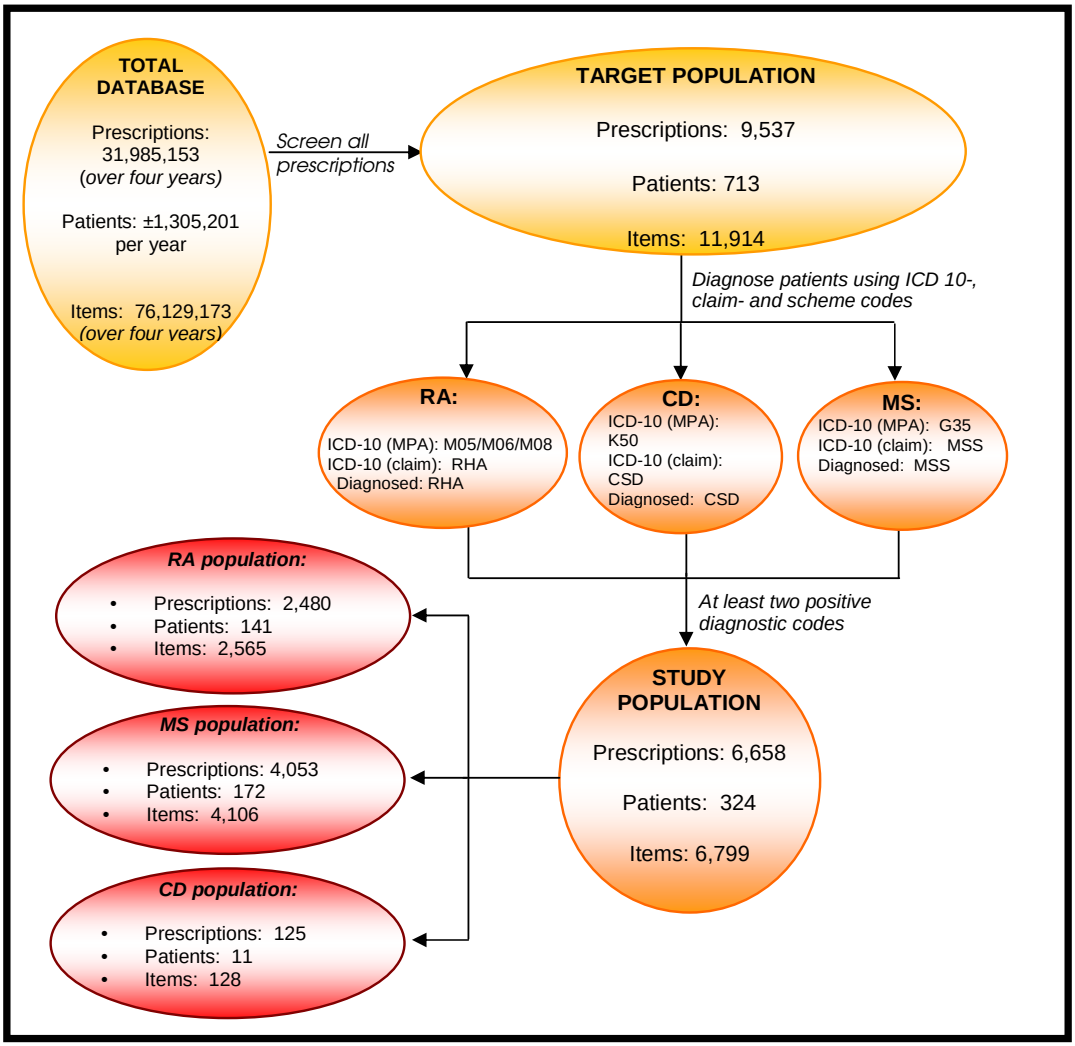

Figure 3.1 Method of selection of the study population from the total database

The study population was further divided into four age groups. As the autoimmune diseases included in this study rarely affect children and persons under the age of twenty (refer to section 2.7.1.2, 2.7.2.2 and 2.7.3.2), the age groups focused on were mainly from the adult population, starting from 25 years of age. The age groups into which the data were divided for the purpose of this study are shown in Table 3.2.

Table 3.2 Age groups for the study population

Group 1	< 25 years
Group 2	25 – 39 years
Group 3	40 – 64 years
Group 4	≥ 65 years

The motivations for the ranges of the groups are the following:

The population of age group one rarely gets affected by the diseases studied in this dissertation (i.e. rheumatoid arthritis, multiple sclerosis and Crohn's disease), but they are not absolutely exempt from being affected, which is why this age group is included (refer to section 2.7). Age group two covers the population in which MS and Crohn's disease usually present themselves and age group three is the main age group that presents with RA for the first time (refer to section 2.7). Age group four is the age group at which point complications from the various diseases most commonly start to develop, especially in the case of RA (with regard to joint damage being so damaged that it may necessitate surgery and replacements) (refer to section 2.7.1.7).

It is currently also protocol to only start treatment with biologics (for RA, MS and Crohn's disease) at a later stage of the disease progression, when all other standard treatments have failed (refer to sections 2.7.1.7, 2.7.2.6 and 2.7.3.6). Since different treatment protocols for different stages of the diseases and thus different age groups exist, evaluations were done accordingly.

3.4 Data analysis

The research data were analysed by making use of a specific software programme i.e. Statistical Analysis System® SAS 9.1.3® (SAS institute Inc., 2002-2003).

Data of the total database as well as the data of the target population were analysed according to four years: 2005 to 2008.

Data of the three study populations (RA, MS and Crohn's disease) were analysed according to three phases: Phase one represents the period between 2005 and 2008 during which the patient only used "other" medicine (non-biological medicine items generally indicated to treat the condition) for his/her condition; phase two represents the period between 2005 and 2008 during which the patient used a biologic immunomodulator to treat his or her condition; and phase three represents the period between 2005 and 2008 during which the patient no longer used a biologic product.

- *Phase one*: medicine items claimed per patient before the first prescription for a biologic immunomodulator was dispensed (any time between 1 January 2005 and 31 December 2008).

- *Phase two*: all the medicines claimed from the date on which the first biologic immunomodulator was dispensed to the patient, to the date on which the last prescription for a biologic was dispensed (between 1 January 2005 and 31 December 2008). Phase two thus consists of biological medicine items as well as other medicine items dispensed during the same period.

- *Phase three*: medicine items claimed after the date on which the last prescription with a biological medicine item had been dispensed.

3.4.1 Classification systems

Different classification systems were used during this study. These are discussed subsequently.

3.4.1.1 Medication

- ***The NAPPI code***

The National Pharmaceutical Pricing Index (NAPPI) code is a unique identifier of pharmaceutical and surgical products (Medicover, 2010). The NAPPI codes consist of a series of numbers and provide information on each individual medicine product. Every medicine item has its own unique NAPPI code, which helps to distinguish between different medicine items, and where applicable, also dosage strength and -forms of products with the same active ingredient (Medicover, 2010).

The NAPPI code is well-established in South Africa as a claiming standard for medicines and surgical products (Medikredit, 2010), and is as a result available as a classification system on the medicine claims database used in this study.

The NAPPI codes of the biological medicines (i.e. adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b and rituximab) were employed to identify the relevant data from the central database.

- ***Active medicine ingredient classification***

Since the medicines investigated in this research project are not included in a single MIMS group, the MIMS classification cannot be used to identify the relevant medicines (Snyman, 2010:10a-12a). Instead, the relevant medicines were identified and classified by their active ingredient. The following active ingredients were selected for investigation:

- Adalimumab,
- Etanercept,
- Infliximab,
- Interferon beta-1a and interferon beta-1b, and
- Rituximab.

These active ingredients were chosen based on various motivations from the literature (refer to section 2.6). The active ingredients were identified through the selection process described in section 3.3.2 and classified as "biologic immunomodulating medicine" for the purpose of this study.

3.4.1.2 Demographic parameters

- ***Age***

The Oxford English Dictionary (1989) defines age as *"a period of existence"* or *"the length of time that anything has existed in its present form or state".*

Since specific age groups are reported to be affected by each of the diseases included in the study, age was included as parameter in this research project.

According to the literature it is mostly adults that are burdened by the autoimmune diseases investigated in this reasearch project (i.e. RA, MS and Crohn's disease) (refer to section 2.7), and therefore the study population was divided into age groups that focus mainly on the adult population (refer to section 3.3.2).

The date of birth as indicated on the database was used to determine a patient's age. A patient's age as it was on the first day of the next year was regarded as his/her age for the current year (i.e. a patient's age on 1 January 2006 was used as his/her age for the whole of 2005) to ensure that patients were included in the same age group for the whole year.

- ***Gender***

Gender is defined by the Cambridge Advanced Learner's Dictionary (2010) as *"the physical and/or social condition of being male or female".*

According to the literature, females are more likely to acquire the diseases investigated in this research project than men (except Crohn's disease that affects women and men equally) (refer to section 2.7.1.2, 2.7.2.2 and 2.7.3.2). Gender will therefore be included as a parameter to analyse the research data of this study to determine whether this is also true in the study population.

3.4.1.3 General parameters

- ***Prescriber type***

The WHO (2003:16) suggests that when drug use is to be determined, the prescriber should be taken into account. To understand how and why medicine is prescribed, it is necessary to analyse the factors that influence prescribing behaviours, because differences between prescribers often cause variations in prescribing patterns that are difficult to explain rationally.

Biologics are generally prescribed by specialists, but may be prescribed by general practitioners. The specialists associated with rheumatoid arthritis are rheumatologists (SARAA, 2008:2), whereas the specialists associated with Crohn's disease and multiple sclerosis are gastroenterologists and neurologists respectively (McQuaid, 2008:547; Multiple sclerosis South Africa, 2010).

The prescriptions for biologic immunomodulators received by patients with rheumatoid arthritis, multiple sclerosis and Crohn's disease were therefore analysed according to the type of prescriber (as indicated on the database) to determine whether biologic immunomodulators are in fact prescribed by specialists (refer to section 4.4).

3.4.2 Descriptive measures

Various elements were identified against which the data could be measured. These measures included the following:

3.4.2.1 Prevalence

Prevalence is defined by the Medical Dictionary (2010) as *"the total number of cases of a given disease in a specified population at a designated time"*, but prevalence can also apply to medicine.

For the purpose of this study, prevalence indicated the total number of patient cases of rheumatoid arthritis, multiple sclerosis and Crohn's disease in the PBM's dataset between January 2005 and December 2008, and it will also be used to indicate the total number of medicine items and prescriptions (both biological and other) claimed for patients during the four study years. In this study, the number of prescriptions (prevalence, *n*), number of medicine items, the average number of medicine items per prescription and average number of prescriptions per patient were determined as listed below:

- All medicine items on the database.
- All relevant biologic immunomodulators (according to active ingredient) claimed for patients with one of the three autoimmune diseases (RA, MS and Crohn's disease).

3.4.2.2 Prescribing patterns

All the prescriptions containing one of the biological medicine items classified as a biologic immunomodulator (refer section 3.3.2) were analysed for prescribing patterns with regard to the following:

- The specific biological medicine item(s) prescribed.
- The treatment received before and after receiving a biologic immunomodulator.
- The number of prescriptions received before, during and after treatment with biologic immunomodulators.
- Other medication prescribed with the biologic immunomodulators.

3.4.2.3 Cost

Vogenberg (2001:3) defines cost as *"the value of resources consumed".*

There are three kinds of costs in all areas of health economics (Walley *et al*., 2004:94):

- ***Direct costs:*** the costs spent directly on the illness, e.g. medicine, hospital and doctors visits, etc. Direct costs are the easiest to measure.
- ***Indirect costs:*** the resources a patient is deprived of because of the illness, e.g. loss of income.
- ***Intangible costs:*** these costs can be considered as the "price" a patient pays for having the illness, e.g. pain and suffering associated with the illness. Intangible costs are very rarely considered when conducting cost studies, as it is a subjective and difficult to measure parameter.

In this study, only the direct costs associated with treatment with biologic immunomodulators were determined. By identifying the costs of the biologic immunomodulators, the financial implication of treatment with these medicines could be determined and expressed in Rand value.

The total costs of the following elements were determined:

- All medicine items and prescriptions on the database.

- All biologic immunomodulating medicine on the database relevant to this study (i.e. adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b and rituximab).
- Medicine treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease.

3.4.3 Statistical analysis

Statistics is defined by Doane and Seward (2007:3) as *"the science of collecting, organising, analysing, interpreting, and presenting data"*, which explains why statistics is also referred to as "data science".

According to Doane and Seward (2007:5) the two principal types of statistics are descriptive and inferential statistics. Banerjee (2003:2) describes descriptive statistics as a statistical technique that involves the description and presentation of data through either charts or graphs, or by making use of numerical summaries, whereas inferential statistics would involve drawing conclusions about the target population from data obtained and analysed from a random sample of that population.

Both descriptive and inferential statistics were used in this study, and the main statistical techniques used to analyse the data included:

- *Descriptive statistics*:
    - Measures of central tendency: ***Arithmetic mean***
    - Measure of spread: ***Standard deviation***
- *Inferential statistics:*
    - ***Cost-prevalence index***
    - ***Effect sizes*** (d-values)

These methods were used to assess the study results and various statistical calculations were applied to aid in the assessment. The following calculations were applied:

3.4.3.1 Arithmetic mean (Average value)

Medhi (1992:53) explains that when a number of observations (denoted by *n*) are obtained from a population, the value of each sample observation is denoted by x. When the sum of the observation values are divided by the number of the values in the set, the arithmetic mean of the dataset is obtained (Agarwal, 2003:37). The arithmetic mean is thus calculated as follows:

$$\overline{x} = \frac{\sum x}{n}$$

Where:

- $\sum$ = sum
- $\overline{x}$ = mean
- x = values of the variables
- n = the number of observations

The mean represents the centre of the set of observations (Medhi, 1992:53).

3.4.3.2 Standard deviation

Snedecor and Cochran (1989:29) describe the standard deviation as *"a measure of the amount of variation among the values of the variables in a population"*. Standard deviation is the best known and most widely used measure of variability, and plays an important role in determining how accurately the average mean can be estimated from a sample of a given size (Ostle & Malone, 1988:62; Snedecor & Cochran, 1989:29).

According to Banerjee (2003:5), standard deviation measures the spread of data around the mean. The value of the standard deviation is thus the average distance of an observation point from the mean (Cohen & Lea, 2004:13; Salkind, 2007:68) and is calculated by means of the equation:

$$s = \sqrt{\frac{\sum \left(x - \bar{x}\right)^2}{n-1}}$$

Where:

- s = standard deviation
- $\sum$ = sum
- x = value of any variable in the dataset
- $\bar{x}$ = mean
- n = the number of observations

3.4.3.3 Cost-prevalence index

Serfontein (1989:180) developed an indicator to determine the ratio between the cost and the prevalence of therapy, called the cost-prevalence index. The equation used to calculate the cost prevalence index in given below:

$$Cost\ \ prevalence\ \ index = \frac{Cost\ (\%)}{prevalence\ \ (\%)}$$

According to Serfontein (1989:180) the value of the cost-prevalence index can be interpreted as follows:

- Cost index value **greater than 1**: utilised therapy is relatively expensive.
- Cost index value **equal to 1**: cost and prevalence of utilised therapy is in equilibrium.
- Cost index value **smaller than 1**: utilised therapy is relatively inexpensive.

The cost-prevalence index was used as an indicator of cost levels of the opposing groups of medicine items used in each research disease, e.g. traditional RA medicine *vs*. biologic RA medicine.

3.4.3.4 Effect sizes / "d"-value

According to Cohen (1988:9) the phrase "effect size" is used to indicate *"the degree to which the phenomenon is present in the population"*. Thalheimer and Cook (2002:3) describe an effect size as the difference between two means divided by the standard deviation of the two variables.

$$d = \frac{\left(\bar{x}_a - \bar{x}_b\right)}{S_{\max}}$$

Where:

- d = Cohen's effect size
- $\bar{x}_a$ = the average medicine treatment cost of *a*
- $\bar{x}_b$ = the average medicine treatment cost of *b*
- $S_{\max}$ = the maximum standard deviation between *a* and *b*

By measuring the effect size of the treatment being studied, researchers can get an indication of the relative magnitude of the treatment, i.e. it indicates the *size* of the treatment's effect. The importance of effect sizes thus lies in their ability to compare the magnitude of different research treatments (Thalheimer & Cook, 2002:2).

The following *d*-values are given by Steyn (1998:3) as guidelines for practical significance:

- Where d = 0.2, it is considered to be a small effect with no significance.
- Where d = 0.5, the effect size is considered to be medium; in this case the effect is observable and may have practical significance.
- Where d = 0.8, the effect is considered to be large and significant, and of practical importance.

3.5 Ethical considerations

Permission to conduct this study was granted by the PBM's board of directors as well as the Ethical Committee of the North-West University. The North-West University granted ethical permission for the study "Investigation of medicine usage patterns in a section of the private health care sector utilising data from a Pharmaceutical Benefit Management company (PBM) in South Africa" and the ethical committee awarded the ethical application number: NWU-0046-08-S5.

Furthermore, patient confidentiality was assured by the PBM by allocating a random, "dummy" member number to each patient. Each prescription record also contained an eleven digit reference number which linked each patient, medical practice or medical aid scheme to line items, and served as a time stamp of when the transaction had been adjudicated.

3.6 Reliability and validity of data

The research data used in this study were directly obtained from the database provided by the PBM. Data were not augmented or manipulated by the researcher in any way. The PBM claims that the data provided are of high quality and standard, and consequently contain reliable and valid information. Data were furthermore verified by testing for outliers and random data checks were preformed. It is therefore the researcher's opinion that research conducted from this data delivered reliable and valid results.

Furthermore, since only one PBM's data were used in this study, no cost or prevalence comparisons could be made, and only the direct cost of medicine was used throughout the study. External validity is limited, which implies that the results obtained from the data analyses can only be generalised to the specific database and the study population.

3.7 Results and discussion

The results and discussion with regard to the empirical investigation of this study will be discussed in Chapter 4 and certain relevant data will be provided in Appendices A and B.

3.8 Conclusions and recommendations

The conclusions and recommendations of this study with specific reference to the general and specific objectives will be discussed in Chapter 5.

3.9 Chapter summary

Various aspects pertaining to the empirical investigation of this study in order to shed light on the specific approaches followed in this research project, were discussed in this chapter.

Chapter four portrays the results of the study and includes various discussions on the data tables.

CHAPTER 4

Results and discussion

Chapter four presents the results of the empirical investigation. Both the data analysis and the study results are discussed in this chapter. Discussions are accompanied by summarised tables to represent the data being discussed.

4.1 Introduction

Chapter four reports on and discusses the results of the empirical study of this research project. Results were obtained from the retrospective analyses of a comprehensive medicine claims database of a pharmacy benefit manager (PBM) for the period ranging from 1 January 2005 to 31 December 2008.

4.1.1 Presentation of the data analysis

Figure 4.1 illustrates the order in which the results of this research project were presented.

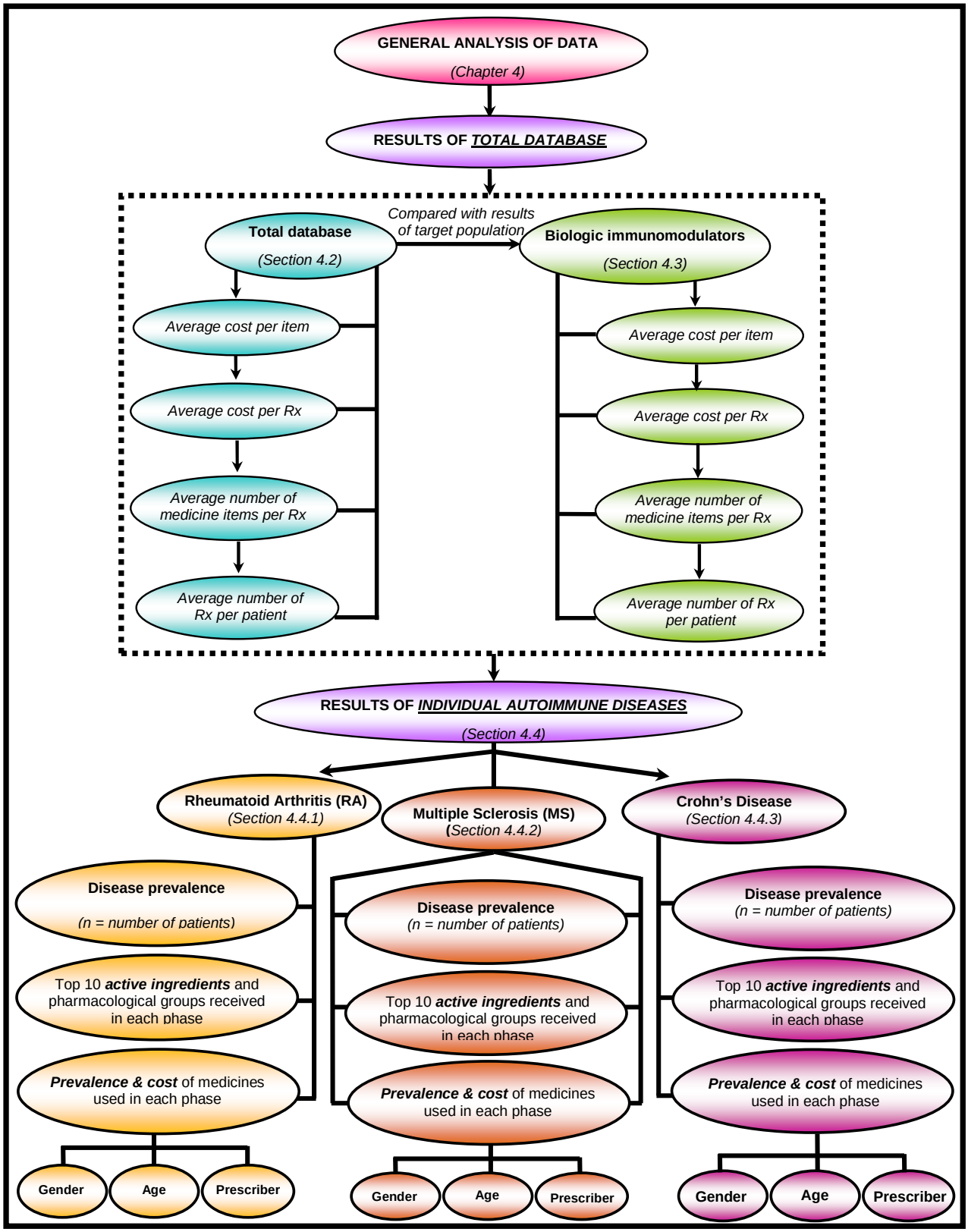

Figure 4.1 Presentation of the results of the data analysis

4.1.2 Definitions

For the purpose of this study, certain terms were standardised and defined. The definitions for the following terms are:

- Total population or total database: *All the beneficiaries on the database.*
- Target population: *All the beneficiaries that received any biologic immunomodulating medicine item (as selected in section 3.4.1.1) at any given time between 1 January 2005 and 31 December 2008.*
- Study population: *All the beneficiaries that received any biologic immunomodulating medicine at any given time between 1 January 2005 and 31 December 2008, and that had had at least two positive diagnostic codes for RA, MS or Crohn's disease.*
- Patient: *A person receiving medication on a prescription. For the purpose of this study, a patient will be defined in section 4.4 as a person with RA, MS or Crohn's disease based on the ICD-10 codes allocated to them during the study period.*
- Prescription: *A written instruction from an authorised prescriber to a pharmacist to dispense a specific medicine item(s). The abbreviation "Rx" is used to refer to a prescription.*
- Medicine item: *An agent or pharmaceutical preparation that contains at least one active ingredient that is used to treat or prevent an illness.*
- Biologic immunomodulating medicine or biologic immunomodulator: For the purpose of this study, a biologic immunomodulator was *any medicine item containing one of the following active ingredients: adalimumab, infliximab, etanercept, rituximab, interferon beta-1a, or interferon beta-1b.*
- Other medicine: *any medicine item that was not a biological medicine item.*
- Trade name: *The name of a medicine item as it is registered at the Medicines Control Council (MCC).*
- Total cost: *The total monetary value that was spent on the medicine item or prescription by the medical aid scheme as well as the patient.*

- Frequency: *The number of times a certain value occurs in a set of data.*

4.1.3 Annotations concerning analysis of the data

The following remarks pertaining to the data analysis would help to explain the researcher's approach and how data results were interpreted:

- Descriptive statistics were used to evaluate and portray the data and inferential statistics were used to draw certain conclusions from the data (refer to section 3.4.3).

- Data represented in the summarised tables and appendices were not manipulated or modified in any way and are a true representation of the data in the original database. Data obtained from the database were assumed to be correct (refer to section 3.6).

- The total data as well as the data of the target population were analysed according to the four years from 1 January 2005 to 31 December 2008.

- The data of RA, MS and Crohn's disease were analysed according to three treatment phases (in section 4.4 of this study) between 2005 and 2008: Phase one represents the period between 2005 and 2008 during which the patient received other medication only (excluding biologics) for his/her condition; phase two represents the period between 2005 and 2008 during which the patient received biologic immunomodulators to treat his or her condition; and phase three represents the period between 2005 and 2008 during which the patient no longer received biological medicine (i.e. the period after the patient had received treatment with biologic immunomodulators) (refer to section 3.4).

- The complete tables of all the research data are given in appendix B. Only a few summarised tables are given in this chapter to aid discussion. Summarised tables do not necessarily contain all available data.

- Some of the tables in this chapter and in the appendices may not add up to one hundred per cent due to rounding off of large decimals. Amounts in the data have been rounded off to the nearest two decimal places.

- For the purpose of this study, frequency and prevalence were regarded as synonyms. Both refer to the number of times medicine items or prescriptions were claimed.

- The top ten pharmacological groups and the top ten active ingredients were identified for each autoimmune condition according to frequency. Where two or more pharmacological groups or active ingredients had the same frequency, they were considered to be tied and more than ten groups or active ingredients were thus included in the table.

- The top ten pharmacological groups and the top ten active medicine ingredients were identified for phase one, phase two and phase three for RA, MS and Crohn's disease.

- As discussed in section 2.10, there are currently no generic products or therapeutic equivalents ("biosimilars") available for biological medicine items. Since generic products are thus not relevant to this study, the trade names of the products were not included as a variable and evaluations were based on active ingredients only.

- The cost on medicine on the database was divided into three amounts, namely "final cost", "final scheme amount" and "final levy". For the purpose of the discussion of data in this study, the total cost of a medicine item or prescription was defined as the "*total cost"*, the amount of the total cost reimbursed by the medical scheme was defined as the "*scheme amount"*, and the amount of the total cost co-paid by the patient was defined as the "*patient levy"*.

- "Cost" only refers to the cost of *medicine*, and does not include expenses such as latex gloves, needles and syringes or any other medical equipment.

- Gender was categorised into three groups, namely F (female), M (male) and U (unknown). The initials F, M and U were used to distinguish between the genders in the tables. Because the value of U is omissible (approximately 0.1% of the total beneficiaries), U was left out of the discussions.

- Patients were divided into four age groups (refer to section 3.3.2). Age groups were assigned numbers 1 to 4 in order to indicate them in the tables.

4.2 Analysis of the database

This section consisted of an analysis of the database. Analyses were done according to different demographic parameters, including gender and age, as well as the type of prescriber. Each analysis included information on three different cost variables, namely average cost, average scheme amount and average patient levy.

4.2.1 General analysis of total database

Section 4.2.1 reflects on the data of the total database for the period 1 January 2005 to 31 December 2008. Table 4.1 is a summary of Tables A.1, A.4, A.7 and A.10 in Appendix B and depicts the data for the total population for each of the years of the study period.

Based on Table 4.1, there was a 35.45% decrease in the number of patients on the total database between 2005 and 2008. The number of patients did increase with 3.21% between 2005 (N = 1,509,621) and 2006 (N = 1,558,090), but then decreased with 37.46% from 2006 to 2008 (N = 974,497).

This change in the data population indicated that the results should be viewed in the context that the study population did not necessarily remain the same over the entire study period due to various reasons, i.e. people change their medical aid schemes, people leave the medical aid scheme and new people join the medical aid scheme, medication changes as new medicine items, treatments and trade names enter the pharmaceutical market, etc.

The average number of prescriptions per patient on the total database was 5.56 ± 6.75 (median = 3.0) in 2005 and increased to 6.95 ± 7.85 (median = 4.0) prescriptions per patient in 2008. This increase was, however, practically insignificant, since the *d*-value between the average number of prescriptions per patient in 2005 and 2008 was only 0.18. The increase in the average number of prescriptions per patient may also be ascribed to changes in medicine therapy or changes in the composition of prescriptions prescribed during each study year.

Based on Table 4.1, a prescription contained an average of two medicine items per prescription per year between 2005 and 2008.

Table 4.1 Summary of the total database

AVERAGE COST PER MEDICINE ITEM				
Year	**Variable**	**Frequency (N = Medicine items)**	**Mean ± SD (R)**	**Total cost (R)**
2005	Total cost	19,500,774	93.32 ± 166.36	1,819,865,251.63
	Scheme amount		82.17 ± 159.21	1,602,447,649.43
	Patient levy		11.15 ± 42.24	217,417,602.20
2006	Total cost	21,113,422	92.82 ± 196.42	1,959,738,734.09
	Scheme amount		80.46 ± 189.99	1,698,709,951.36
	Patient levy		12.36 ± 45.28	261,028,782.73
2007	Total cost	19,075,724	100.56 ± 324.11	1,918,284,176.66
	Scheme amount		84.66 ± 304.10	1,615,007,032.92
	Patient levy		15.90 ± 101.24	303,277,143.74
2008	Total cost	16,439,253	108.63 ± 436.75	1,785,871,013.85
	Scheme amount		89.94 ± 419.97	1,478,548,228.92
	Patient levy		18.69 ± 107.16	307,322,784.93
AVERAGE COST PER PRESCRIPTION				
Year	**Variable**	**Frequency (N = Prescriptions)**	**Mean ± SD (R)**	**Total cost (R)**
2005	Total cost	8,391,836	216.86 ± 342.30	1,819,865,251.63
	Scheme amount		190.95 ± 323.66	1,602,447,649.43
	Patient levy		25.91 ± 81.07	217,417,602.20
2006	Total cost	8,906,348	220.04 ± 395.22	1,959,738,734.09
	Scheme amount		190.73 ± 377.73	1,698,709,951.36
	Patient levy		29.31 ± 88.47	261,028,782.73
2007	Total cost	7,911,096	242.48 ± 600.31	1,918,284,176.66
	Scheme amount		204.14 ± 564.37	1,615,007,032.92
	Patient levy		38.34 ± 171.45	303,277,143.74
2008	Total cost	6,775,873	263.56 ± 789.01	1,785,871,013.85
	Scheme amount		218.21 ± 756.95	1,478,548,228.92
	Patient levy		45.36 ± 181.31	307,322,784.93

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION			
Year	**Frequency (N = Prescriptions)**	**Average medicine items per Rx Mean ± SD**	**Total number of medicine items**
2005	8,391,836	2.32 ± 1.52	19,500,774
2006	8,906,348	2.37 ± 1.55	21,113,422
2007	7,911,096	2.41 ± 1.59	19,075,724
2008	6,775,873	2.43 ± 1.64	16,439,253

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT			
Year	**Frequency (N = Patients)**	**Average Rx per patient Mean ± SD**	**Total number of prescriptions**
2005	1,509,621	5.56 ± 6.75	8,391,836
2006	1,558,090	5.72 ± 6.96	8,906,344
2007	1,178,596	6.71 ± 7.55	7,911,084
2008	974,497	6.95 ± 7.85	6,775,863

Between 2005 and 2006, both the number of prescriptions and medicine items claimed increased. Based on Table 4.1, there was an 8.27% and a 6.13% increase in the number of medicine items and the number of prescriptions respectively between 2005 and 2006. After 2006, both the number of medicine items and prescriptions claimed decreased. There was a 22.14% decrease in the number of medicine items and a 23.92% decrease in the number of prescriptions from the end of 2006 to the end of 2008. The total number of medicine items and prescriptions claimed decreased between 2005 and 2008 because the total number of patients also decreased during this period. Figure 4.2 illustrates the increase and decrease in the total number of patients and prescriptions over the four-year period.

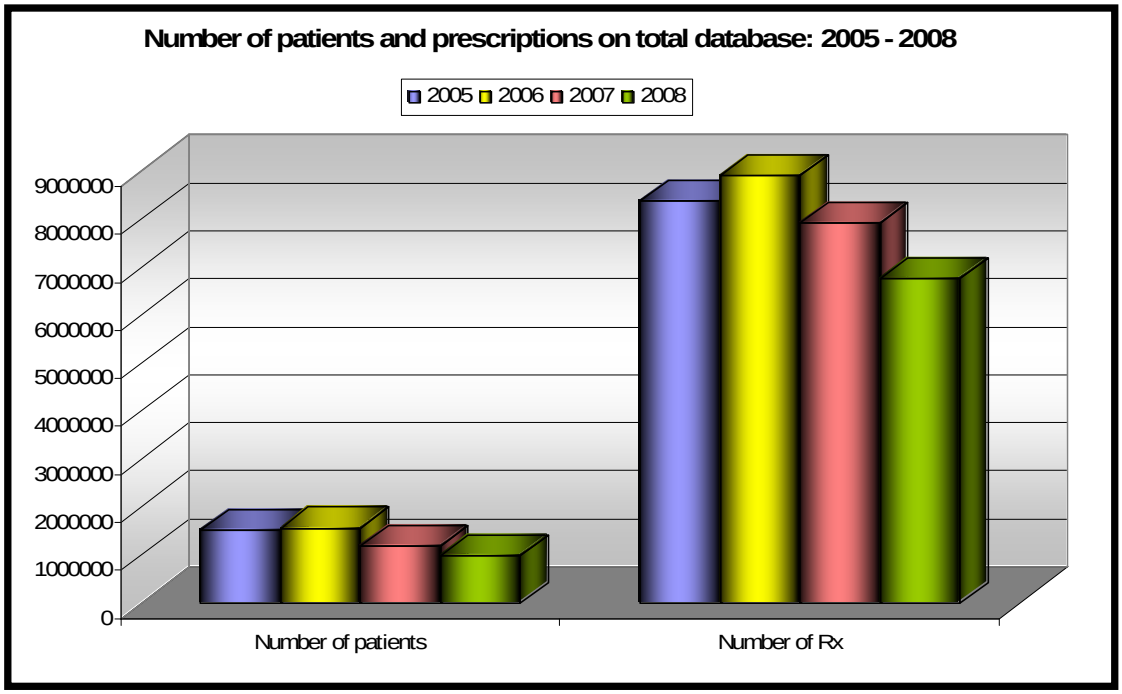

Figure 4.2 Number of patients and prescriptions on the total database between 2005 and 2008

Based on Table 4.1, the average cost per medicine item increased with 16.41% from 2005 (R93.32 ± 166.36) (median = R52.57) to 2008 (R108.63 ± 436.75) (median = R59.30) and the average cost per prescription increased with 21.53% from 2005 (R216.86 ± 342.30) (median = R135.40) to 2008 (R263.56 ± 789.01) (median = R151.56). The increase in the average cost per medicine item and the average cost per prescription was not practically significant, since the *d*-values between the average costs of 2005 and 2008 were 0.03 and 0.06 respectively. The average scheme amount per prescription increased with 14.28% from 2005 (R190.95 ± 323.66) (median = R116.54) to 2008 (R218.21 ± 756.95) (median = R118.74), whereas the average patient levy (patient's co-payment) also increased with 75.07%, from R25.91 ± R81.07 (median = R0.00) in 2005 to R45.36 ± R181.31 (median =

R11.79) in 2008 (refer to Table 4.1). The increase in the average scheme amount was not practically significant, since the *d*-value between the average scheme amount in 2005 and 2008 was only 0.04. The increase in the average patient levy was larger than the increase in the average scheme amount, but was still not practically significant (*d*-value = 0.12).

The reason why the average cost per medicine item and the average cost per prescription increased from 2005 to 2008 could be ascribed (among other factors) to the increase in the price of consumer products (which also include medicine) and medical inflation. The reason why the increase in the average patient levy was greater than the increase in the average scheme amount might be because medical aid schemes are shifting the cost burden to patients in response to escalating health care costs (refer to section 1.1).

The results indicated that the total medicine cost for the total database for the four respective years was relatively equal, with minor fluctuations between consecutive years. There was a 7.69% increase in the total medicine expenditure between 2005 and 2006, but after 2006 the total medicine expenditure per year decreased with 2.16% (2006 to 2007) and 7.41% (2007 to 2008) (refer to Table 4.1). The increase in the total medicine expenditure between 2005 and 2006 could be ascribed to the increase in the number of patients, medicine items and prescriptions during this time, and the decrease in the total medicine expenditure from 2006 until 2008 was probably due to the decrease in the number of patients, prescriptions and medicine items on the total database between 2006 and 2008.

4.2.2 Analysis of total database according to demographic parameters

The demographic parameters according to which the data will be discussed in this section, are gender and age (refer to section 3.3.2 and section 4.1.3).

Since the frequency and cost trends of medicine items were similar to those of prescriptions (refer to section 4.2.1), the frequency and cost of medication were only discussed on the hand of prescriptions in this section, but the trends also applied to medicine items.

4.2.2.1 Analysis according to gender

As explained in paragraph 4.1.2, patients were divided into males and females. Those patients whose gender was not indicated on the database were labelled “unknown” and were

not discussed as the value is omissible (n = 1,730 in 2005; n = 1,108 in 2006 and n = 407 and n = 0 in 2008).

4.2.2.1.1 Analysis of claims made for female patients

This section discusses the analysis of the female population of the database. Tables 4.2.1 and 4.2.2 summarise tables A.2, A.5, A.8 and A.11 in appendix B. The percentages shown in Table 4.2.1 show what percentage of the total patient population, total number of prescriptions and total number of medicine items are represented by females. Percentages were calculated by dividing the frequency (n) in Table 4.2.1 by the frequency (N) of the corresponding heading in Table 4.1. Percentage values of Table 4.2.1 thus represent that portion of the values of the total database contributed by female patients.

Table 4.1 shows a total number of 1,509,621 patients on the database in 2005. According to Table 4.2.1, 55.80% of these patients were female (n = 842,386). In 2006, a total of 1,558,090 patients featured on the database of which 55.77% (n = 868,891) were females. In 2007 the female population represented 55.52% (n = 654,348) of the total patient population (N = 1,178,596) and in 2008 there were 974,497 patients on the total database, of which 55.23% (n = 538,254) were female. The percentage of the total patient population represented by female patients thus decreased from 2005 to 2008 with 0.57%, which might be because the total patient population decreased during this period and female patients represented the larger percentage of the total patient population.

The percentage prescriptions claimed by females fluctuated slightly between 2005 and 2008 – increasing and decreasing with small percentages every alternative year. Out of the 8,391,836 prescriptions that were claimed in 2005, 60.02% (n = 5,036,494) of all prescriptions were claimed for female patients. In 2006, the female population claimed 59.91% (n = 5,336,203) of the total number of prescriptions (N = 8,906,348) claimed that year – a decrease of 0.11% from the previous year. Of the total 7,911,096 prescriptions claimed in 2007, 60.10% (n = 4,754,911) were claimed by female patients, which meant a 0.19% increase from 2006 (refer to Table 4.2.1).

Table 4.2.1 Summary of total database according to females

AVERAGE COST PER ITEM						
Year	**Gender**	**Variable**	**Frequency (n = Medicine items)**	**% medicine items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**F**	Total cost	11,750,190	60.25	92.31 ± 158.69	1084,626,865.29
		Scheme amount			80.65 ± 151.40	947,688,793.44
		Patient levy			11.65 ± 41.24	136,938,071.85
2006	**F**	Total cost	12,699,707	60.15	91.52 ± 188.12	1162,254,536.29
		Scheme amount			78.66 ± 181.38	999,015,475.00
		Patient levy			12.85 ± 45.46	163,239,061.29
2007	**F**	Total cost	11,509,346	60.34	98.89 ± 300.67	1138,188,990.86
		Scheme amount			82.46 ± 286.55	949,029,333.61
		Patient levy			16.44 ± 83.42	189,159,657.25
2008	**F**	Total cost	9,893,928	60.18	106.86 ± 416.84	1057,274,453.63
		Scheme amount			87.52 ± 397.36	865,959,792.23
		Patient levy			19.34 ± 116.02	191,314,661.40

AVERAGE COST PER PRESCRIPTION						
Year	**Gender**	**Variable**	**Frequency (n = Prescriptions)**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**
2005	**F**	Total cost	5,036,494	60.02	215.35 ± 330.75	1084,626,865.29
		Scheme amount			188.16 ± 310.90	947,688,793.44
		Patient levy			27.19 ± 80.87	136,938,071.85
2006	**F**	Total cost	5,336,203	59.91	217.81 ± 380.43	1162,254,536.29
		Scheme amount			187.21 ± 361.56	999,015,475.00
		Patient levy			30.59 ± 89.95	163,239,061.29
2007	**F**	Total cost	4,754,911	60.10	239.37 ± 559.98	1138,188,990.86
		Scheme amount			199.59 ± 530.41	949,029,333.61
		Patient levy			39.78 ± 148.33	189,159,657.25
2008	**F**	Total cost	4,062,385	59.95	260.26 ± 752.96	1057,274,453.63
		Scheme amount			213.17 ± 716.56	865,959,792.23
		Patient levy			47.09 ± 195.17	191,314,661.40

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Gender**	**Frequency (n = Prescriptions)**	**Mean ± SD (Medicine items)**	**Total number of medicine items**
2005	**F**	5,036,494	2.33 ± 1.54	11,750,190
2006	**F**	5,336,203	2.38 ± 1.58	12,699,707
2007	**F**	4,754,911	2.42 ± 1.62	11,509,346
2008	**F**	4,062,385	2.44 ± 1.67	9,893,928

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT					
Year	**Gender**	**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**F**	842,386	55.80	5.98 ± 7.16	5,036,494
2006	**F**	868,891	55.77	6.14 ± 7.37	5,336,202
2007	**F**	654,348	55.52	7.27 ± 7.99	4,754,911
2008	**F**	538,254	55.23	7.55 ± 8.32	4,062,385

In 2008, 0.15% less prescriptions were claimed for female patients than in 2007, i.e. 59.95% (n = 4,602,385) of the total number of prescriptions claimed (N = 974,497) in 2008 had been for female patients (refer to Table 4.2.1). There furthermore was a 23.98% decrease in the number of prescriptions and an 18.76% decrease in the number of medicine items claimed for female patients from 2005 to 2008. Based on Table 4.2.1, a female patient received between five and eight prescriptions per year with an average of two medicine items per prescription between 2005 and 2008.

The average cost per prescription for a female patient increased with 1.14% between 2005 and 2006, and again with 9.90% between 2006 and 2007, but decreased with 8.73% from 2007 to 2008. The average prescription cost for female patients thus increased with 20.85% from 2005 (R215.35 ± 330.75) (median = R135.36) to 2008 (R260.26 ± 752.96) (median = R151.67). The *d*-value (0.06), however, indicated that this increase was not practically significant. The average scheme amount decreased between 2005 and 2006 with 0.50%, but increased with 6.61% between 2006 and 2007 and with 6.80% between 2007 and 2008. The average patient levy increased each year between 2005 and 2008. The average patient levy increased with 73.19% from 2005 to 2008, which was more than ten times greater than the increase in the average scheme amount over the same period (refer to Table 4.2.1).

The total medicine expenditure towards females for 2005 was R1, 084,626,865.29 which contributed to 59.60% of the total medicine expenditure (N = R1, 819,865,251.63) for that year. In 2006 the total cost for medication claimed for females added up to R1,162,254,536.29 and contributed to 59.31% of the total medication cost (N = R1,959,738,734.09) for that year. The total medication cost for female patients in 2007 amounted to R1, 138,188,990.86. Medication for females thus contributed to 59.33% of the total medication cost (N = R 1,918,284,176.66) for 2007 and to 59.20% (n = R1, 057,274,453.63) of the total medicine expenditure (N = R 1,785,871,013.85) for 2008. The total medicine expenditure toward female patients thus decreased with 0.4% from 2005 to 2008 (refer to Table 4.2.1).

4.2.2.1.2 Analysis of claims made for male patients

This section discusses the analysis of the male population of the database. The percentages shown in Table 4.2.2 indicate what percentages of the total patient population, total number of prescriptions and total number of medicine items were represented by males.

Table 4.2.2 Summary of total database according to males

AVERAGE COST PER MEDICINE ITEM						
Year	**Gender**	**Variable**	**Frequency (n = Medicine items)**	**% medicine items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**M**	Total cost	7,734,461	39.66	94.87 ± 176.88	733,769,633.85
		Scheme amount			84.48± 169.85	653,370,941.06
		Patient levy			10.39 ± 43.72	80,398,692.79
2006	**M**	Total cost	8,403,158	39.80	94.77 ± 208.10	796,360,401.04
		Scheme amount			83.15 ± 202.04	698,682,181.29
		Patient levy			11.62 ± 45.01	97,678,219.75
2007	**M**	Total cost	7,562,466	39.64	103.08 ± 356.74	779,508,488.81
		Scheme amount			88.00 ± 328.91	665,466,500.10
		Patient levy			15.08 ± 123.54	114,041,988.71
2008	**M**	Total cost	6,545,325	39.82	111.32 ± 465.21	728,596,560.22
		Scheme amount			93.59 ± 451.99	612,588,436.69
		Patient levy			17.72 ± 92.16	116,008,123.53
AVERAGE COST PER PRESCRIPTION						
Year	**Gender**	**Variable**	**Frequency (n = Prescriptions)**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**
2005	**M**	Total cost	3,348,219	39.90	219.15 ± 358.17	733,769,633.85
		Scheme amount			195.14 ± 341.05	653,370,941.06
		Patient levy			24.01 ± 81.38	80,398,692.79
2006	**M**	Total cost	3,565,331	40.03	223.36 ± 416.16	796,360,401.04
		Scheme amount			195.97 ± 400.43	698,682,181.29
		Patient levy			27.40 ± 86.20	97,678,219.75
2007	**M**	Total cost	3,154,367	39.87	247.12 ± 656.34	779,508,488.81
		Scheme amount			210.97 ± 611.87	665,466,500.10
		Patient levy			36.15 ± 201.38	114,041,988.71
2008	**M**	Total cost	2,713,488	40.04	268.51 ± 840.07	728,596,560.22
		Scheme amount			225.76 ± 813.62	612,588,436.69
		Patient levy			42.75 ± 158.27	116,008,123.53

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRITPION TOTAL DATABASE				
Year	**Gender**	**Frequency (*n* = Rx)**	**Mean ± SD (Medicine items)**	**Total number of medicine items**
2005	**M**	3,348,219	2.31 ± 1.47	7,734,461
2006	**M**	3,565,331	2.36 ± 1.50	8,403,158
2007	**M**	3154367	2.40 ± 1.55	7,562,466
2008	**M**	2,713,488	2.41 ± 1.59	6,545,325

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT					
Year	**Gender**	**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**M**	665,505	44.08	5.03 ± 6.15	3,348,219
2006	**M**	688,091	44.16	5.18 ± 6.35	3,565,328
2007	**M**	523,841	44.45	6.02 ± 6.90	3,154,355
2008	**M**	436,243	44.77	6.22 ± 7.15	2,713,478

Table 4.2.2 shows that male patients represented 44.08% (n = 665,505) of the total database population (N = 1,509,621) in 2005. In 2006, male patients represented 44.16% (n = 688,091) of the total database population (N = 1,558,090), and in 2007 males represented 44.45% (n = 523,841) of all patients on the database (N = 1,178,596). In 2008, 44.77% (n = 436,243) of all the patients on the database (N = 974,497) were males. The percentage of the total database represented by males thus increased with 0.69% from 2005 to 2008, in response to the decrease in the percentage patients represented by females.

In 2005, 39.90% (n = 3,348,219) of a total number of prescriptions claimed (N = 8,391,836) through the PBM were claimed for male patients. The percentage prescriptions claimed for males increased with 0.13% from 2005 to 2006 since 40.03% (n = 3,565,331) of the total number of prescriptions (N = 8,906,348) claimed in 2006 were claimed for males. In 2007, male patients' prescriptions contributed to 39.87% (n = 3,154,367) of all the prescriptions (N = 7,911,096) claimed, which was 0.16% less than in 2006, whereas in 2008, 40.04% (n = 2,713,488) of a total number of prescriptions (N = 6,775,873) claimed were claimed for male patients, which was 0.17% more than the year before. Between 2005 and 2008, male patients claimed between five and seven prescriptions per year, and each prescription had an average of two medicine items (refer to Table 4.2.2).

The average cost per prescription for a male patient increased each year during the four-year study period. The average prescription cost increased with 1.92% between 2005 and 2006, with 10.64% between 2006 and 2007 and with 8.66% between 2007 and 2008 – a total increase of 22.52% in four years. The *d*-value indicated (0.06) that the increase in the average prescription cost for male patients from 2005 (R219.15 ± 358.17) (median = R135.53) to 2008 (R268.51 ± 840.07) (median = R151.40) was not practically significant. The average scheme amount per prescription increased with a total of 15.69% between 2005 and 2006 and the average patient levy increased with 78.05% from 2005 to 2008 (refer to Table 4.2.2). The increase in the average scheme amount and the average patient levy was not practically significant (*d*-values = 0.04 and 0.12 respectively). Based on Table 4.2.2, the total cost of medication for male patients contributed to 40.32% (n = R733, 769,633.85) of the total medicine expenditure (N = R1, 819,865,251.63) in 2005, whereas in 2006, the total medication cost for males contributed to 40.64% (n = R796, 360,401.04) of the total medicine expenditure (N = R1, 959,738,734.09). The total cost of medication for males (n = R779, 508,488.81) in 2007, contributed to 40.64% of the total medicine cost (N = R1, 918,284,176.66), and in 2008, 40.80% (n = R779, 508,488.81) of the total medicine expenditure (N = R1, 785,871,013.85) was spent on prescriptions claimed for male patients. The percentage of the total medicine expenditure spent on males thus increased with 0.48% from 2005 to 2008 (refer to Table 4.2.2).

4.2.2.1.3 Summary of analysis of total database according to gender

According to Tables 4.2.1 and 4.2.2 the patient population of the total database was not equally distributed between male and female genders. Tables 4.2.1 and 4.2.2 indicated that the female population represented approximately 11% more of the total population of the database each year than the male population. This is, however, in accordance with the gender distribution of the South African population. According to the 2001 population census done by Statistics South Africa, 52.17% (n = 23,385,500) of the total population of South Africa (N = 44,829,309) were female, whereas 47.81% (n = 21,433,809) were male (Statistics South Africa, 2001). In the mid-year population estimates for 2009, Statistics South Africa also estimated that in 2009, 52% (approximately 25, 45 million) of the population would be female (Statistics South Africa, 2009:3). The appearance of a larger percentage females than males in the research database is thus a close representation of the total population of South Africa.

Tables 4.2.1 and 4.2.2 showed that females represented about 55% of the total patient population each year between 2005 and 2008 (55.80% in 2005; 55.77% in 2006; 55.52% in 2007 and 55.23% in 2008), whereas males represented about 44% (44.08% in 2005; 44.16% in 2006; 44.45% in 2007 and 44.77% in 2008), but the percentage of the total patient population represented by females decreased from 2005 to 2008 (and the percentage patients represented by males increased in response), which might be ascribed to the fact that the total patient population decreased from 2005 to 2008 and most patients of the database population were female.

Both the percentage of prescriptions and the percentage of medicine items claimed each year were larger for the female population than for the male population. Claims for female patients represented approximately 60% of all the medicine items and prescriptions each year, whereas claims for male patients represented the remaining ~40% of the medicine items and prescriptions each year, which was expected since there were more females on the database than males. The total number of medicine items and prescriptions claimed for both males and females, decreased from 2005 to 2008, most likely because the number of patients on the database (both males and females) also decreased during this period.

There was not a large difference in the average number of prescriptions claimed each year between males and females – female patients received between five and eight prescriptions per year, and male patients received between five and seven prescriptions per year (*d*-value = 0.16). Both male and female patients received an average of two medicine items per prescription between 2005 and 2008.

The average cost per prescription for a male and a female patient was approximately the same between 2005 and 2008, and the average cost per prescription increased for both males and females from 2005 to 2008. The increase in the average medication cost might be ascribed to an increase in the price of consumer products and medical inflation. Furthermore, the increase in the average patient levy per prescription for both males and females was greater than the increase in the average scheme amount, which could be based on the perception that the cost burden of health care is shifting from payers and purchasers (medical aid schemes) to patients (refer to section 1.1) because of rising health care costs.

On the other hand, the larger part (around 60%) of the total annual medicine expenditure was spent on female patients between 2005 and 2008, but this was not unexpected, since the larger part of the data population consisted of females. The total medicine expenditure on both males and females, however, decreased from 2005 to 2008 in response to the decrease in the total medicine expenditure of the database between 2005 and 2008 (refer to Tables 4.2.1 and 4.2.2) because of the decrease in the total number of patients, medicine items and prescriptions from 2005 to 2008.

4.2.2.2 Analysis according to age

The patient population of the database was divided into four age groups: the first age group includes all the patients younger than 25 years; the second age group includes all patients aged between 25 and 39 years; age group three includes patients older than 39 years but younger than 65 years; and age group four includes all patients aged 65 years and older. In this section the total database was analysed according to each age group. Age groups were numbered “1” to “4” in Tables 4.3.1 to 4.3.4., which were all summarised from Tables A.3, A.6, A.9 and A.12 in Appendix B.

4.2.2.2.1 Analysis of age group 1 (< 25 years)

This section includes a discussion of the analysis of age group one of the database. The percentages shown in Table 4.3.1 show what percentage of the total patient population, total number of prescriptions and total number of medicine items were represented by patients younger than 25 years.

Table 4.3.1 Summary of total database according to age group 1

AVERAGE COST PER MEDICINE ITEM						
Year	**Age group**	**Variable**	**Frequency (n = Medicine items)**	**% medicine items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**1**	Total cost	3,658,580	18.76	65.54 ± 101.13	239,766,846.41
		Scheme amount			58.74 ± 95.32	214,897,939.98
		Patient levy			6.80 ± 29.14	24,868,906.43
2006	**1**	Total cost	3,912,699	18.53	64.95 ± 113.93	254,141,563.62
		Scheme amount			56.77 ± 107.71	222,111,395.73
		Patient levy			8.19 ± 33.36	32,030,167.89
2007	**1**	Total cost	3,346,576	17.54	68.42 ± 163.51	228,982,535.62
		Scheme amount			57.11 ± 146.54	191,117,985.47
		Patient levy			11.31 ± 66.36	37,864,550.15
2008	**1**	Total cost	2,421,518	14.73	75.49 ± 210.85	182,794,294.08
		Scheme amount			61.95 ± 201.09	150,022,179.26
		Patient levy			13.53 ± 51.49	32,772,114.82
AVERAGE COST PER PRESCRIPTION						
Year	**Age group**	**Variable**	**Frequency (n = Prescriptions)**	**% Prescriptions**	**Mean ± SD (R)**	**Total cost (R)**
2005	**1**	Total cost	1,552,841	18.50	154.41 ± 190.13	239,766,846.41
		Scheme amount			138.39 ± 179.38	214,897,939.98
		Patient levy			16.02 ± 53.97	24,868,906.43
2006	**1**	Total cost	1,633,373	18.34	155.59 ± 213.41	254,141,563.62
		Scheme amount			135.98 ± 201.78	222,111,395.73
		Patient levy			19.61 ± 63.22	32,030,167.89
2007	**1**	Total cost	1,397,144	17.66	163.89 ± 292.33	228,982,535.62
		Scheme amount			136.79 ± 259.00	191,117,985.47
		Patient levy			27.10 ± 122.80	37,864,550.15
2008	**1**	Total cost	1,034,765	15.27	176.65 ± 365.21	182,794,294.08
		Scheme amount			144.98 ± 345.12	150,022,179.26
		Patient levy			31.67 ± 90.49	32,772,114.82

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Age group**	**Frequency (*n* = Rx)**	**Mean ± SD (Medicine items)**	**Total number of medicine items**
2005	**1**	1,552,841	2.36 ± 1.33	3,658,580
2006	**1**	1,633,373	2.40 ± 1.35	3,912,699
2007	**1**	1,397,144	2.40 ± 1.36	3,346,576
2008	**1**	1,034,765	2.34 ± 1.36	2,421,518

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT					
Year	**Age group**	**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**1**	493,907	32.72	3.14 ± 3.32	1,552,841
2006	**1**	499,442	32.05	3.27 ± 3.46	1,633,373
2007	**1**	394,672	33.49	3.54 ± 3.68	1,397,144
2008	**1**	293,599	30.13	3.52 ± 3.78	1,034,765

Based on Table 4.3.1, age group one represented 32.72% (n = 493,907) of all the patients on the database in 2005 (N = 1,509,621). In 2006, age group one represented 32.05% (n = 499,442) of the total database population (N = 1,558,090) (0.7% less than the previous year), and in 2007 age group one represented 33.49% (n = 394,672) of the total data population (N = 1,178,596) (1.44% more than in 2006). The percentage patients in age group one decreased with 3.36% between 2007 and 2008, as only 30.13% (n = 293,599) of a total number of patients on the database (N = 974,497) were under the age of 25 in 2008. Between 2005 and 2008 there was a total decrease of 2.59% in patients under the age of 25 relative to the total database.

The number of prescriptions claimed for patients in age group one (n = 1,552,841) contributed to 18.50% of the total number of prescriptions (N = 8,391,836) claimed in 2005. In 2006, the percentage prescriptions claimed for this age group remained roughly the same, as the total number of prescriptions (n = 1,633,373) claimed in 2006 contributed to 18.34% of the total number of prescriptions (N = 8,906,348). Between 2006 and 2008, the percentage prescriptions claimed by patients younger than 25 years decreased with 3.07%, as only 17.66% (n = 1,397,144) and 15.27% (n = 1,034,765) of the total number of prescriptions claimed in 2007 (N = 7,911,096) and 2008 (N = 6,775,873) respectively, had been for patients in age group one. Patients in age group one claimed between three to four prescriptions per year in the four-year period, with an average of two medicine items per prescription (refer to Table 4.3.1).

From 2005 to 2006, the average cost per prescription for patients younger than 25 years increased with 0.76%. From 2006 to 2007, there was a 5.33% increase in the average prescription cost, and another 7.79% increase from 2007 to 2008. The average prescription cost for patients in age group one thus increased with a total of 14.40% from 2005 (R154.41 ± 190.13) (median = R103.79) to 2008 (R176.65 ± 365.21) (median = R109.94). Once again, the increase in the average prescription cost was not practically significant (*d*-value = 0.06). The average scheme amount per prescription decreased with 1.77% from 2005 to 2006, but then increased with 0.60% from 2006 to 2007, and again with 5.99% from 2007 to 2008 – which gives a total increase of 4.76% in four years. The increase in the average scheme amount was not practically significant, since the *d*-value between the average scheme amount in 2005 and the average scheme amount in 2008 was only 0.019. The increase in the average patient levy during the four years was greater than the increase in the average scheme amount: there was a 22.41% increase in the average patient levy from 2005 to 2006, and a 38.19% increase from 2006 to 2007. The average patient levy increased with 97.69% between 2005 and 2008 (an increase of more than twenty times the increase in the amount paid by the medical aid scheme), but the increase was also not practically significant

since the *d*-value between the average patient levy in 2005 and 2008 was only 0.17 (refer to Table 4.3.1). Based on Table 4.3.1, the total amount spent on medication for age group one decreased with a small percentage each year. The medicine expenditure on age group one was R239, 766,846.41 in 2005, which was 13.17% of the total medicine expenditure of that year. With a total cost of R254, 141,563.62, medication claimed for patients younger than 25 years contributed to 12.97% of the total amount spent on medication in 2006. In 2007, the total amount spent on medication for patients in age group one added up to R228, 982,535.62, which represented 11.94% of the total medicine expenditure for that year, whereas the total cost of medication for age group one represented 10.24% (n = R182,794,294.08) of the total medication cost for 2008. The percentage of the total medicine expenditure represented by patients under the age of 25 years thus decreased with 2.93% from 2005 to 2008 (refer to Table 4.3.1).

4.2.2.2.2 Analysis of age group 2 (25 – 39 years)

This section contains a discussion of the analysis of age group two of the database. The percentages in Table 4.3.2 show what percentage of the total data population, total number of prescriptions and total number of medicine items were represented by patients between the ages of 25 and 39 years.

Based on Table 4.3.2, patients in age group two represented 19.33% (n = 291,872) of the total database population (N = 1,509,621) in 2005. This percentage did not change much in 2006 when age group two represented 19.26% (n = 300,056) of the total database population (N = 1,558,090). In 2007, patients between 25 and 39 years represented 17.22% (n = 202,901) of the total number of patients on the database (N = 1,178,596) (which was 2.04% less than in 2006), and from 2007 to 2008 there was another 1.52% decrease in the percentage patients in age group two, since patients between 25 and 39 years represented only 15.70% (n = 152,974) of total number of patients on the database (N = 974,497) in 2008.

In 2005, 15.73% (n = 1,319,940) of the total number of prescriptions claimed through the PBM (N = 8,391,836) had been claimed for patients in age group two. In 2006, 15.35% (n = 1,367,117) of all the prescriptions claimed that year were claimed for patients between the ages of 25 and 39 years, whereas only 14.06% (n = 1,112,243) of a total number of prescriptions (N = 7,911,096) were claimed for age group two in 2007 (refer to Table 4.3.2).

Table 4.3.2 Summary of total database according to age group 2

AVERAGE COST PER MEDICINE ITEM						
Year	**Age group**	**Variable**	**Frequency (n = Medicine items)**	**% items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**2**	Total cost	2,930,322	15.03	77.40 ± 148.62	226,818,610.94
		Scheme amount			70.12 ± 142.95	205,479,491.44
		Patient levy			7.28 ± 36.32	21,339,119.50
2006	**2**	Total cost	3,068,900	14.54	76.47 ± 169.84	234,674,113.15
		Scheme amount			67.96 ± 163.44	208,554,713.53
		Patient levy			8.51 ± 41.72	26,119,399.62
2007	**2**	Total cost	2,528,016	13.25	81.77 ± 263.69	206,723,414.80
		Scheme amount			69.79 ± 252.80	176,421,796.24
		Patient levy			11.99 ± 66.83	30,301,618.56
2008	**2**	Total cost	1,876,874	11.42	90.16 ± 363.99	169,227,300.16
		Scheme amount			75.70 ± 345.02	142,085,583.63
		Patient levy			14.46 ± 97.47	27,141,716.53
AVERAGE COST PER PRESCRIPTION						
Year	**Age group**	**Variable**	**Frequency (n = Prescriptions)**	**% Prescriptions**	**Mean ± SD (R)**	**Total cost (R)**
2005	**2**	Total cost	1,319,940	15.73	171.84 ± 289.74	226,818,610.94
		Scheme amount			155.67 ± 278.26	205,479,491.44
		Patient levy			16.17 ± 66.25	21,339,119.50
2006	**2**	Total cost	1,367,117	15.35	171.66 ± 315.33	234,674,113.15
		Scheme amount			152.55 ± 302.11	208,554,713.53
		Patient levy			19.11 ± 74.62	26,119,399.62
2007	**2**	Total cost	1,112,243	14.06	185.86 ± 470.34	206,723,414.80
		Scheme amount			158.62 ± 449.21	176,421,796.24
		Patient levy			27.24 ± 115.07	30,301,618.56
2008	**2**	Total cost	836,129	12.34	202.39 ± 631.89	169,227,300.16
		Scheme amount			169.93 ± 597.93	142,085,583.63
		Patient levy			32.46 ± 159.88	27,141,716.53

AVERAGE NUMBER OF ITEMS PER PRESCRIPTION				
Year	**Age group**	**Frequency (*n* = Rx)**	**Mean ± SD (Items)**	**Total number of medicine items**
2005	**2**	1,319,940	2.22 ± 1.33	2,930,322
2006	**2**	1,367,117	2.24 ± 1.35	3,068,900
2007	**2**	1,112,243	2.27 ± 1.37	2,528,016
2008	**2**	836,129	2.24 ± 1.37	1,876,874

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT					
Year	**Age group**	**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**2**	291,872	19.33	4.52 ± 5.09	1,319,940
2006	**2**	300,056	19.26	4.56 ± 5.25	1367,114
2007	**2**	202,901	17.22	5.48 ± 5.74	1,112,243
2008	**2**	152,974	15.70	5.37 ± 5.89	836,129

In 2008 the percentage prescriptions claimed for this group decreased further with 1.76%, as only 12.34% (n = 836,129) of the total number of prescriptions (N = 6,775,873) claimed in 2008 were for patients in age group two. Between 2005 and 2008, an average of between four and six prescriptions was claimed for patients in age group two per year, with an average of two medicine items per prescription (refer to Table 4.3.2).

The average cost per prescription for patients in age group two increased with 17.78% from 2005 (R171.84 ± 289.74) (median = R105.55) to 2008 (R202.39 ± 631.89) (median = R108.54). The average cost per prescription first decreased with 0.10% between 2005 and 2006, but increased each year thereafter. The *d*-value (0.05) indicates that the 17.78% increase in the average prescription cost for patients in age group two was practically insignificant. The average scheme amount per prescription also decreased at first, when this amount declined with 2.05% between 2005 and 2006, but after 2006 however, there was a 3.98% increase in the average scheme amount per prescription for age group two patients, and another 7.13% increase between 2007 and 2008. The average scheme amount per prescription thus increased with a total of 9.16% between 2005 and 2008 for patients between the ages of 25 and 39 years. This 9.16% increase is, however, considerably lower than the 100.74% increase in the average patient levy from 2005 to 2008 (refer to Table 4.3.2). The *d*-values of increases in the average scheme amount (0.02) and the average patient levy (0.1) from 2005 to 2008 indicated that these increases were not large or significant (refer to Table 4.3.2).

Based on Table 4.3.2, the percentage of the total medicine expenditure spent on age group two decreased each year. In 2005, the total cost of medication for age group two contributed 12.46% (n = R226, 818,610.94) of the total medication cost for 2005. In 2006, the total amount spent on medication for age group two contributed 11.97% (n = R234, 674,113.15) of the total medicine expenditure; 0.49% less than the year before. The total medication cost for 2007 contributed 10.78% (n = R206, 723,414.80) of the total amount spent on medication that year, whereas only 9.48% (n = R169, 227,300.16) of the total medication costs for 2008 went towards patients between the ages of 25 and 39 years.

4.2.2.2.3 Analysis of age group 3 (40 – 64 years)

This section presents the analysis of age group three of the database. The percentages shown in Table 4.3.3 show what percentages of the total patient population, total number of prescriptions and total number of medicine items were represented by patients between 40 and 64 years.

Table 4.3.3 Summary of total database according to age group 3

AVERAGE COST PER MEDICINE ITEM						
Year	**Age group**	**Variable**	**Frequency (n = Medicine item)**	**% items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**3**	Total cost	8,363,409	42.89	97.08 ± 176.48	811,952,830.36
		Scheme amount			86.21 ± 169.38	721,025,658.60
		Patient levy			10.87 ± 45.59	90,927,171.76
2006	**3**	Total cost	9,261,669	43.87	96.15 ± 209.04	890,470,151.20
		Scheme amount			84.33 ± 203.00	781,008,788.47
		Patient levy			11.82 ± 46.52	109,461,362.73
2007	**3**	Total cost	8,494,142	44.53	103.40 ± 353.70	878,327,951.34
		Scheme amount			88.40 ± 334.16	750,921,044.36
		Patient levy			15.00 ± 101.86	127,406,906.98
2008	**3**	Total cost	7,639,419	46.47	109.54 ± 466.22	836,842,632.27
		Scheme amount			92.09 ± 450.59	703,481,122.70
		Patient levy			17.46 ± 109.70	133,361,509.57

AVERAGE COST PER PRESCRIPTION						
Year	**Age group**	**Variable**	**Frequency (n = Prescription)**	**% Prescriptions**	**Mean ± SD (R)**	**Total cost (R)**
2005	**3**	Total cost	3,669,930	43.73	221.24 ± 358.41	811,952,830.36
		Scheme amount			196.47 ± 341.04	721,025,658.60
		Patient levy			24.78 ± 84.72	90,927,171.76
2006	**3**	Total cost	3,968,128	44.55	224.41 ± 416.63	890,470,151.20
		Scheme amount			196.82 ± 400.70	781,008,788.47
		Patient levy			27.59 ± 89.14	109,461,362.73
2007	**3**	Total cost	3,563,317	45.04	246.49 ± 649.89	878,327,951.34
		Scheme amount			210.74 ± 616.78	750,921,044.36
		Patient levy			35.76 ± 167.99	127,406,906.98
2008	**3**	Total cost	3,172,135	46.82	263.81 ± 839.12	836,842,632.27
		Scheme amount			221.77 ± 810.00	703,481,122.70
		Patient levy			42.04 ± 182.14	133,361,509.57

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Age group**	**Frequency (*n* = Rx)**	**Mean ± SD (Items)**	**Total number of medicine items**
2005	**3**	3,669,930	2.28 ± 1.48	8,363,409
2006	**3**	3,968,128	2.33 ± 1.51	9,261,669
2007	**3**	3,563,317	2.38 ± 1.56	8,494,142
2008	**3**	3,172,135	2.41 ± 1.59	7,639,419

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT					
Year	**Age group**	**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**3**	556,022	36.83	6.60 ± 7.29	3,669,930
2006	**3**	588,107	37.75	6.75 ± 7.46	3,968,127
2007	**3**	447,503	37.97	7.96 ± 7.94	3,563,317
2008	**3**	400,575	41.11	7.92 ± 7.97	3,172,125

Table 4.3.3 shows that age group three represented 36.83% (n = 556,022) of the total patient population (N = 1,509,621) in 2005. In 2006, age group three represented 37.75% (n = 588,107) of the total patient population (N = 1,558,090) and in 2007, 37.97% (n = 447,503) of the total number of patients on the database (N = 974,497) was represented by patients between the ages of 40 and 64 years. By 2008, 41.11% (n = 400,575) of the total patient population (N = 974,497) was represented by age group three. The percentage of the total population represented by patients between the ages of 40 and 64 years of age thus increased with 4.28% from 2005 to 2008.

In 2005, the prescriptions claimed by patients in age group three represented 43.73% (n = 3,669,930) of the total number of prescriptions (N = 8,391,836) claimed through the PBM that year. Prescriptions claimed for patients between the ages of 40 and 64 years represented 44.55% (n = 3,968,127) of the total prescriptions claimed in 2006 (N = 8,906,248), and 45.04% (n = 3,563,317) of the total number of prescriptions claimed in 2007 (N = 7,911,096). In 2008, 46.82% (n = 3,172,125) of the total number of prescriptions (N = 6,775,873) claimed that year had been claimed for patients in age group four. The percentage prescriptions claimed for patients between 40 and 64 years thus increased with 3.09% from 2005 to 2008. During the four-year period, a patient in age group three received between six and eight prescriptions per year and a prescription claimed for a patient in age group three contained an average of two medicine items (refer to Table 4.3.3).

The average cost per prescription for a patient in age group three increased with 19.24% from 2005 (R221.24 ± 358.41) (median = R140.38) to 2008 (R263.81 ± 839.12) (median = R151.53), but the increase was not practically significant (*d*-value = 0.05). The average scheme amount per prescription for patients between 40 and 64 years increased with 12.88% from 2005 to 2008, whereas the average patient levy increased with 69.65% over the four years. Even though the increase in the average patient levy was considerably larger than the increase in the average scheme amount, the *d*-values indicate that neither increase was practically significant (*d*-values = 0.03 and 0.09 respectively) (refer to Table 4.3.3).

The percentage of the total medication cost contributed by age group three also did not change significantly between 2005 and 2008. Prescriptions claimed for patients between 40 and 64 years in 2005 contributed 44.62% (R811, 952,830.36) of the total medicine expenditure for that year. In 2006, medication claimed for age group three contributed 45.44% (R890,470,151.20) of the total medication cost for that year, and in 2007 the total cost of this age group's medication contributed 45.79% (R878,327,951.34) of the total amount spent on prescriptions in that year. Prescriptions claimed for patients between the

ages of 40 and 64 years contributed to 46.86% of the total medicine expenditure for 2008, which was 2.24% higher than in 2005 (refer to Table 4.3.3).

4.2.2.2.4 Analysis of age group 4 (≥ 65 years)

This section presents a discussion on the analysis of age group four of the database. The percentages shown in Table 4.3.4 show what percentages of the total patient population, total number of prescriptions and total number of medicine items were represented by patients older than 64 years.

Based on Table 4.3.4, patients older than 64 years represented 11.12% (n = 167,820) of the total patient population (N = 1,509,621) in 2005. In 2006, 10.94% (n = 170,485) of the total patient population (N = 1,558,090) was represented by age group four. From 2006 to 2007, the percentage of patients older than 64 years increased slightly, as 11.33% (n = 133,520) of the total number of patients on the database were older than 64 years in 2007. Table 4.3.4 shows that there was a further increase in the percentage patients represented by age group four between 2007 and 2008, as 13.07% (n = 127,349) of the total patient population were represented by age group four in 2008. The percentage of the total patient population of the database represented by patients older than 64 years thus increased with 1.95% from 2005 to 2008.

In 2005, 22.03% (n = 1,849,125) of the total number of prescriptions claimed in that year (N = 8,391,836) had been claimed for patients older than 64 years, and in 2006, 21.76% (n = 1,937,730) of the total number of prescriptions (N = 8,906,348) had been claimed for this age group. In 2007, 23.24% (n = 1,838,380) of the total number of prescriptions (N = 7,911,096) had been claimed for patients in age group four, whereas in 2008, 25.57% (n = 1,732,844) of the total number of prescriptions on the database had been for patients aged 65 years and older. Between 2005 and 2008, between 11 and 14 prescriptions were claimed for patients older than 64 years per year, with each prescription containing an average of two medicine items (refer to Table 4.3.4). This was considerably more than the average number of prescriptions claimed for patients younger than 64 during the same period. The reason why patients in age group four received more prescriptions per patient per year might be because older people (geriatrics) are usually affected with diseases like urinary incontinence, degenerative osteoarthritis, osteoporosis, Parkinsonism, polymyalgia rheumatica, temporal arteritis etc. for which medication is received each month of the year (Beers, 2006:2760).

Table 4.3.4 Summary of total database according to age group 4

AVERAGE COST PER MEDICINE ITEM						
Year	**Age group**	**Variable**	**Frequency (n = Medicine items)**	**% items**	**Mean ± SD (R)**	**Total cost (R)**
2005	**4**	Total cost	4,548,463	23.32	119.01 ± 193.54	541,326,963.92
		Scheme amount			101.36 ± 185.77	461,044,559.41
		Patient levy			17.65 ± 47.19	80,282,404.51
2006	**4**	Total cost	4,870,154	23.07	119.19 ± 232.49	580,452,906.12
		Scheme amount			100.00 ± 225.84	487,035,053.63
		Patient levy			19.18 ± 52.07	93,417,852.49
2007	**4**	Total cost	4,706,990	24.68	128.37 ± 376.68	604,250,274.90
		Scheme amount			105.49 ± 350.11	496,546,206.85
		Patient levy			22.88 ± 131.19	107,704,068.05
2008	**4**	Total cost	4,501,442	27.38	132.63 ± 497.24	597,006,787.34
		Scheme amount			107.29 ± 476.82	482,959,343.33
		Patient levy			25.34 ± 126.73	114,047,444.01
AVERAGE COST PER PRESCRIPTION						
Year	**Age group**	**Variable**	**Frequency (n = Prescriptions)**	**% Prescriptions**	**Mean ± SD (R)**	**Total cost (R)**
2005	**4**	Total cost	1,849,125	22.03	292.75 ± 419.52	541,326,963.92
		Scheme amount			249.33 ± 394.46	461,044,559.41
		Patient levy			43.42 ± 97.67	80,282,404.51
2006	**4**	Total cost	1,937,730	21.76	299.55 ± 492.37	580,452,906.12
		Scheme amount			251.34 ± 470.10	487,035,053.63
		Patient levy			48.21 ± 109.03	93,417,852.49
2007	**4**	Total cost	1,838,392	23.24	328.68 ± 720.57	604,250,274.90
		Scheme amount			270.10 ± 671.64	496,546,206.85
		Patient levy			58.59 ± 227.46	107,704,068.05
2008	**4**	Total cost	1,732,844	25.57	344.52 ± 927.44	597,006,787.34
		Scheme amount			278.71 ± 887.57	482,959,343.33
		Patient levy			65.82 ± 223.52	114,047,444.01
AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION						
Year	**Age group**		**Frequency (*n* = Rx)**		**Mean ± SD (Items)**	**Total number of medicine items**
2005	**4**		1,849,125		2.46 ± 1.82	4,548,463
2006	**4**		1,937,730		2.51 ± 1.87	4,870,154
2007	**4**		1,838,392		2.56 ± 1.91	4,706,990
2008	**4**		1,732,844		2.60 ± 1.95	4,501,442
AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT						
Year	**Age group**		**Frequency (n = Patients)**	**% patients**	**Mean ± SD (Rx)**	**Total number of prescriptions**
2005	**4**		167,820	11.12	11.02 ± 10.19	1,849,125
2006	**4**		170,485	10.94	11.37 ± 10.54	1,937,730
2007	**4**		133,520	11.33	13.77 ± 10.72	1,838,380
2008	**4**		127,349	13.07	13.61 ± 10.93	1,732,844

The average cost per prescription for a patient in age group four increased each year between 2005 and 2008, with a total percentage increase of 17.68% from 2005 (R292.75 ± 419.52) (median = R193.63) to 2008 (R344.52 ± 927.44) (median = R210.28). This increase in the average prescription cost was not practically significant (*d*-value = 0.06). The increase in the average scheme amount was 11.78% between 2005 and 2008, whereas the average patient levy increased with 51.59% during the four years.

The total medication cost for patients in age group four contributed to 29.75% (n = R541, 326,963.92) of the total medicine expenditure (N = R1, 819,865,251.63) for 2005, whereas 29.62% (n = R580, 452,906.12) of the total medication cost for 2006 (N = R1, 959, 738,734.09) was spent on medication for patients aged 65 years and older. The percentage contribution to the total annual medicine expenditure of age group four increased with 1.88% between 2006 and 2007, as 31.50% (n = R604, 250,274.90) of the total medicine expenditure (N = R1, 918,284,176.66) was towards age group four. The total medication cost for patients older than 64 years decreased to R597, 006,787.34 in 2008, but the percentage contribution of age group four toward the total medicine expenditure for that year increased to 33.43% (refer to Table 4.3.4).

4.2.2.2.5 Summary of analysis of total database according to age

From the various analyses done above, it is evident that as for the gender groups, the four age groups into which the total database was divided were not equal with regard to percentage distribution of the patient population.

Patients between 40 and 64 years of age represented the largest percentage of the total patient population (between 36.83% and 41.11%) each year between 2005 and 2008. Patients younger than 25 years represented the second largest percentage (between 30.13% and 33.49%) of the total patient population, followed by patients between the ages of 25 and 39 years, who represented between 15.70% and 19.33% of the total patient population of the database between 2005 and 2008. Patients older than 64 years subsequently represented the smallest percentage (between 10.94% and 13.07%) of the total patient population during the four study years. The total number of patients in each age group decreased from 2005 to 2008 because the total number of patients on the database decreased (see section 4.2.1). The percentages of the total patient population represented by age groups one and two decreased from 2005 to 2008, whereas the percentage represented by age groups three and four increased. Thus, as patients got older each year, several patients moved on to the next age group (i.e. a patient who had been 39 years in

2005, was included in age group two, but in 2006 when the patient was 40 years old, he/she was included in age group three, etc.). The largest percentage (between 43.73% and 46.82%) of the total number of prescriptions each year was claimed for patients between the ages of 40 and 64 years. This was expected, as this age group also represented the largest percentage of the total number of patients on the database. It was also expected that claims for patients between the ages of 25 and 39 years represented only between 12.34% and 15.73% of the total number of prescriptions claimed each year, since age group two represented only a small percentage of the total patient population. However, it was unexpected that the second largest percentage (between 22.03% and 25.57%) of the total number of prescriptions was claimed for patients older than 64 years, since age group four represented the smallest percentage of the total number of patients on the database. Furthermore, the second lowest percentage (15.27% to 18.50%) of the total number of prescriptions each year was claimed for patients younger than 25 years, who represented the second highest percentage of the total patient population (refer to Table 4.3.5).

This phenomenon is, however, explained when the average number of prescriptions per patient is taken into account. Patients in age group four received the most prescriptions per year on average – between 11.02 ± 10.19 (2005) and 13.61 ± 10.93 (2008) prescriptions per patient per year, whereas patients in age group one received the lowest number of prescriptions per year – between 3.14 ± 3.32 (2005) and 3.52 ± 3.78 (2008) prescriptions per year. Age group three and age group two claimed an average of between 6.60 ± 7.29 (2005) and 7.92 ± 7.97 (2008), and 4.52 ± 5.09 (2005) and 5.37 ± 5.89 (2008) respectively, these being in accordance with their percentage contributions to the total number of prescriptions claimed (refer to Table 4.3.5).

Patients between 40 and 64 years, as could be expected, contributed the largest percentage (between 44.62% and 46.86%) to the total medicine expenditure each year, whereas patients older than 64 years contributed the second largest percentage (between 29.75% and 33.43%) of the total medication cost for each year. This makes sense since the largest percentage of medicine items and prescriptions were claimed for patients older than 39 years between 2005 and 2008. Age groups one and two displayed the smallest percentages of the total medicine expenditure each year (refer to Table 4.3.5). The different contributions to the total annual medication costs are further explained by the average cost per prescription per age group. Not only did patients older than 64 years receive the highest number of prescriptions per year, but their prescriptions also had the highest average cost (which might be ascribed to the use of relatively expensive chronic medication throughout the year). Table 4.3.5 shows how the average prescription cost for patients in each age group differed between 2005 and 2008. Based on Table 4.3.5, prescriptions for patients younger than 40

years (age groups one and two) had the lowest average cost between 2005 and 2008, whereas prescriptions for patients older than 39 but younger than 64 years had the second highest cost, and prescriptions for patients older than 64 years had the highest average cost.

Table 4.3.5 Average cost per prescription according to age groups

	Age group 1		Age group 2		Age group 3		Age group 4	
	Average	Median	Average	Median	Average	Median	Average	Median
2005	154.41 ± 190.13	103.79	171.84 ± 289.74	105.55	221.24 ± 358.41	140.38	292.75 ± 419.52	193.63
2006	155.59 ± 213.41	102.61	171.66 ± 315.33	101.92	224.41 ± 416.63	138.41	299.55 ± 492.37	193.69
2007	163.89 ± 292.33	104.62	185.86 ± 470.34	104.86	246.49 ± 649.89	146.93	328.68 ± 720.57	207.89
2008	176.65 ± 365.21	109.94	202.39 ± 631.89	108.54	263.81 ± 839.12	151.53	344.52 ± 927.44	210.28

The *d*-values calculated between the average costs per prescription for each age group indicated that the differences in the average prescription cost between the different age groups were not practically significant (*d*-values were below 0.4 each year). Furthermore, the average cost per prescription increased for each age group every year, but the highest increase in the average prescription cost was for age group three, which had a total increase of 19.24% between 2005 and 2008 (refer to Table 4.3.5).

The average scheme amount and the average patient levy also increased for each age group, but the increase in the average patient levy was far more than the increase in the average scheme amount or even the total cost per prescription. The outsized increase in the average patient levy in comparison to the increase in the average scheme amount might be contributed to the notion that medical aid schemes are shifting the cost burden of increasing health care costs to patients (refer to section 1.1). Furthermore, the greatest increase in the average patient levy per prescription was for patients younger than 40 years, whose patient levy per prescription increased with 100.74% (patients older than 25 years) and 97.69% (patients younger than 25 years) respectively. This might be ascribed to the perception that patients younger than 40 years seldom receive chronic medication for conditions on the chronic disease list, which is part of the prescribed minimum benefits (PMB), but mostly receive acute medication. Since medical aid schemes are obligated to pay for PMB in full, medical aid schemes cannot shift the cost burden of chronic medication to patients, and thus makes up for it by shifting a larger percentage of the cost burden of acute medication to patients, which might be why the average patient levy for patients in age groups one and two increased more than for age groups three and four.

4.3 Analysis of the target population

The following section deals with an analysis of the target population of the database. The target population includes all those patients who have received any one of the biologic immunomodulating medicines (adalimumab, etanercept, infliximab, rituximab, interferon beta-1a and interferon beta-1b) at least once during the study period (1 January 2005 to 31 December 2008).

The data analysis in this section was conducted as a comparison between the data of the total database and the data of the target population in order to determine what percentages of the frequencies and/or costs of the medicine items and prescriptions that were claimed through the PBM between 2005 and 2008 were represented by biologic immunomodulating medicines. The target population was discussed according to two demographic parameters, gender and age, and each parameter was divided into groups (refer to section 4.1.3). Figure 4.3 illustrates how the results of the analysis of the target population were presented.

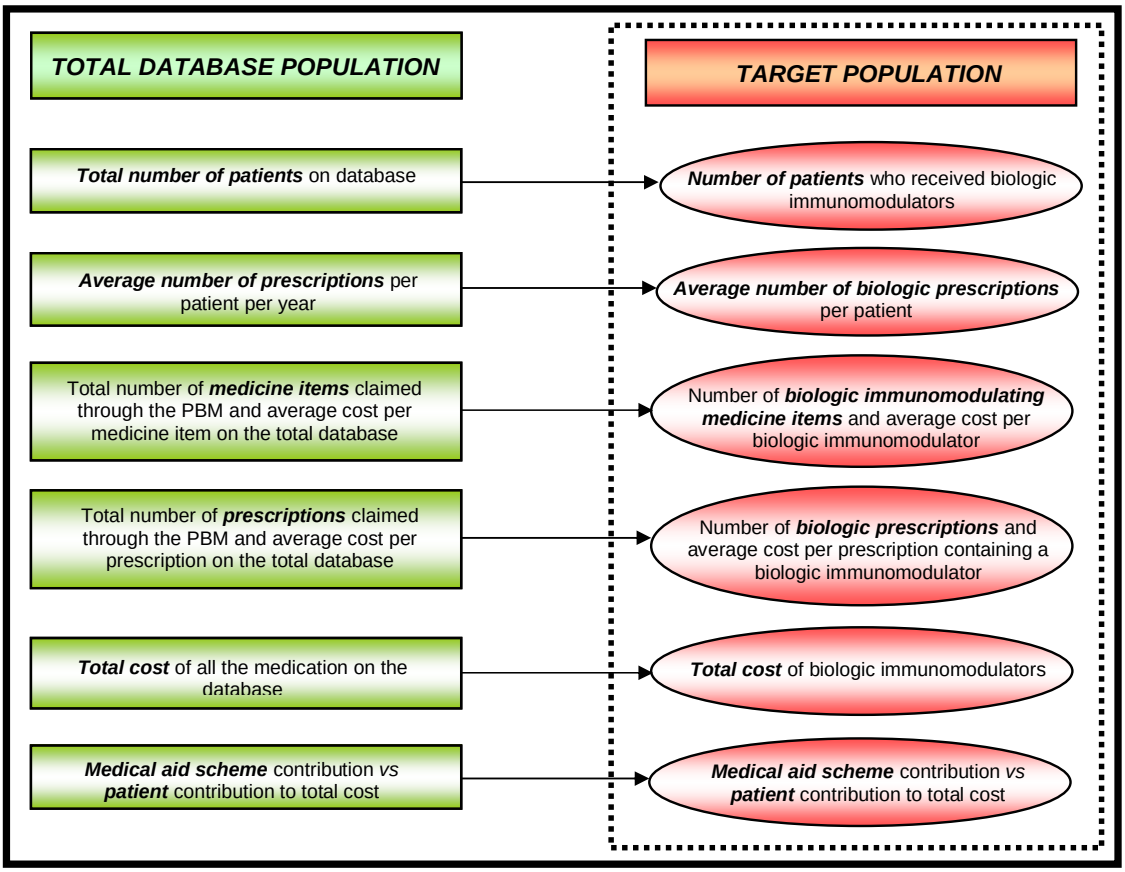

Figure 4.3 Presentation of the results of section 4.3

4.3.1 General analysis of the target population

Tables 4.4.1 to 4.4.9 summarise and compare the frequencies and costs of the six biologic immunomodulating medicine items relevant to this study with the frequencies and costs of all the medicine items in the total database between 2005 and 2008. In the context of this section of the study, the term "biologics" refers to all the medicine items with one of the following active ingredients:

- Adalimumab,
- Etanercept,
- Infliximab,
- Interferon beta-1a,
- Interferon beta-1b, and
- Rituximab.

The analysis of the target population was done as outlined in Figure 4.3 and the results were presented accordingly.

4.3.1.1 Number of patients and the average number of prescriptions per patient per year

Table 4.4.1 shows the number of patients and the average number of prescriptions per patient per year for both the total database and target population.

Table 4.4.1 Number of patients and average number of prescriptions per patient per year: total database *vs* target population

TOTAL DATABASE				BIOLOGIC IMMUNOMODULATORS				
Year	Frequency (n = Patients)	Total number of prescriptions	Average Rx per patient Mean ± SD	Year	Frequency (n = Patients)	% n	Total number of prescriptions	Average Rx per patient Mean ± SD
2005	1,509,621	8,391,836	5.56 ± 6.75	*2005*	198	0.013	1,319	6.66 ± 5.00
2006	1,558,090	8,906,344	5.72 ± 6.96	*2006*	279	0.018	2,054	7.36 ± 4.50
2007	1,178,596	7,911,084	6.71 ± 7.55	*2007*	372	0.032	2,971	7.99 ± 4.49
2008	974,497	6,775,863	6.95 ± 7.85	*2008*	416	0.042	3,193	7.68 ± 4.77

% n = $n_{biologic\ immunomodulators}$ / $n_{total\ database}$ x 100

According to Table 4.4.1, there were 1,509,621 patients on the total database in 2005, of which 0.013% (n = 198) received biologics. In 2006, the frequency of patients who received biologics did not increase very much, as only 0.018% (n = 279) of the total patient population (N = 1,558,090) received biologics. The number of patients who received biologics increased with 0.014% from 2006, to 2007, when 0.032% (n = 372) of the total patient population (N = 1,178,596) received these medicine items. From 2007 to 2008, the number of patients who received biologics increased with another 0.01%, as 0.042% (n = 416) of the total population (N = 974,497) received these medicine items in 2008. In a four year period, the percentage of the total population who received biologics thus increased with 0.024%, even though the total patient population of the database decreased from 2005 to 2008 (refer to section 4.2.1).

Based on Table 4.4.1, the average number of prescriptions per patient for the total database was between five and seven prescriptions per patient per year, whereas a patient who received prescriptions for biologics received an average of between six and eight prescriptions per year. The higher number of biologics prescriptions per patient per year implicates a possible higher number of biological medicine items claimed per year which in turn might implicate a possible increase in the medication cost.

Figure 4.4.1 indicates what portion of the total patient population of the database received biologic immunomodulators between 2005 and 2008, whereas Figure 4.4.2 illustrates how the average number of prescriptions per patient per year for the total database compared to the average number of prescriptions per patient who received biologic immunomodulators per year.

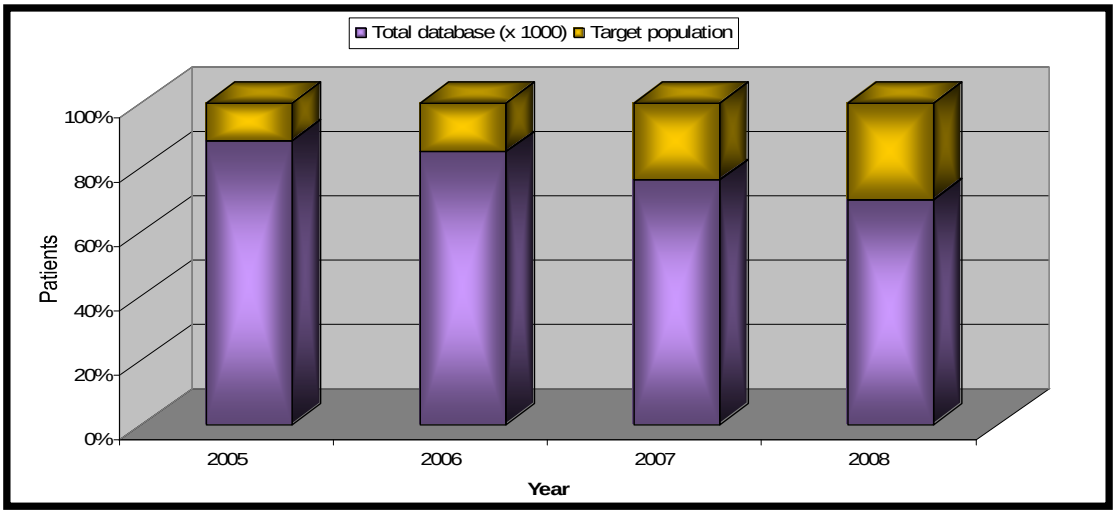

Figure 4.4.1 Portion of the total patient population of the database who received biologic immunomodulators between 2005 and 2008

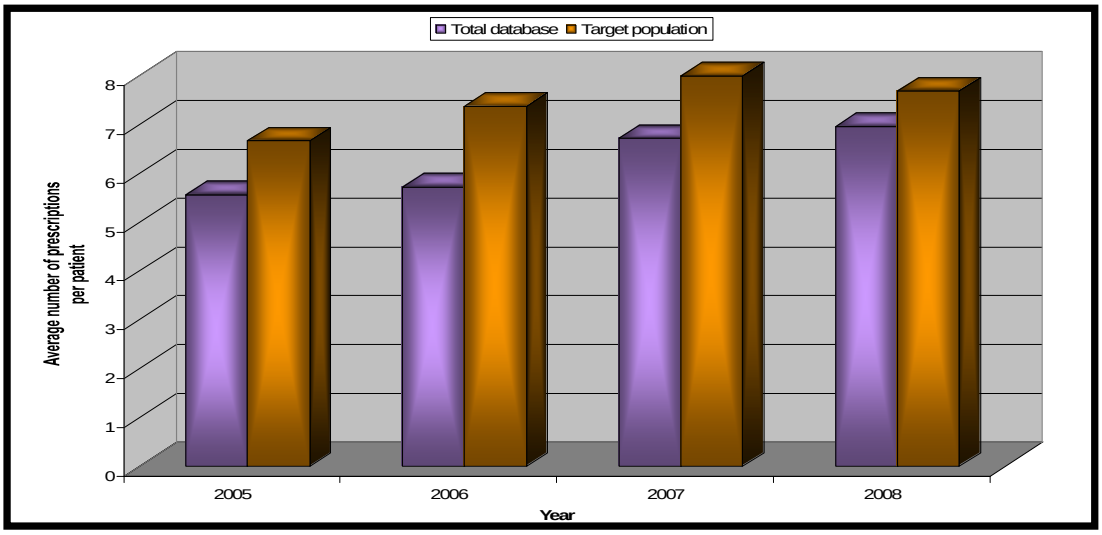

Figure 4.4.2 Average number of prescriptions per patient for total database compared to average number of prescriptions per patient for target population

4.3.1.2 Number of medicine items and average cost per medicine item

The average cost per medicine item on the total database and the average cost per biologic immunomodulating medicine item for the period 1 January 2005 to 31 December 2008 are summarised in Table 4.4.2. The percentage values (%n) in Table 4.4.2 show what portion of the total number of medicine items on the database was represented by biologic immunomodulators each year, whereas Figure 4.5 graphically illustrates the difference in the average cost of a biologic immunomodulating medicine item and the average cost of a medicine item on the total database.

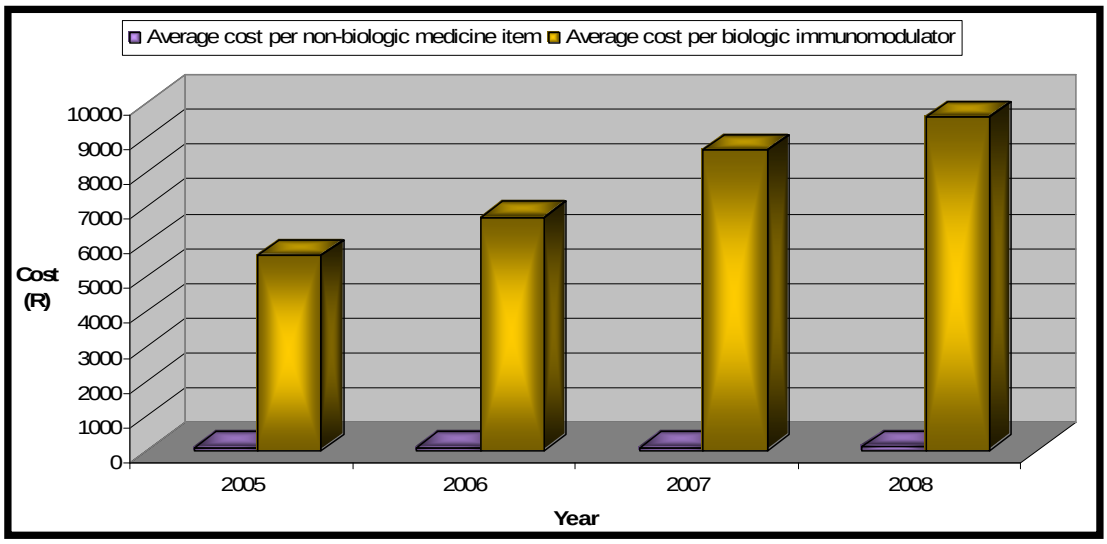

Figure 4.5 Average cost per biologic immunomodulator *vs* average cost per medicine item on the total database

Table 4.4.2 Number of medicine items and average cost per medicine item: total database *vs* target population

AVERAGE COST PER MEDICINE ITEM FOR TOTAL DATABASE					AVERAGE COST PER MEDICINE ITEM FOR BIOLOGIC IMMUNOMODULATORS						
Year	**Variable**	**Frequency (n = medicine item)**	**Mean ± SD (R)**	**Total cost (R)**	**Year**	**Variable**	**Frequency (n = medicine item)**	**% n**	**Mean ± SD (R)**	**Total cost (R)**	**% R**
2005	Total cost	19,500,774	93.32 ± 166.36	1,819,865,251.63	***2005***	Total cost	1,759	0.009	5602.71 ± 2166.61	9,855,161.01	0.54
	Scheme amount		82.17 ± 159.21	1,602,447,649.43		Scheme amount			5398.44 ± 2299.56	9,495,851.34	
	Patient levy		11.15 ± 42.24	217,417,602.20		Patient levy			204.27 ± 1050.60	359,309.67	
2006	Total cost	21,113,422	92.82 ± 196.42	1,959,738,734.09	***2006***	Total cost	2,829	0.013	6698.90 ± 1990.97	18,951,176.69	0.97
	Scheme amount		80.46 ± 189.99	1,698,709,951.36		Scheme amount			6560.42 ± 2125.64	18,559,432.28	
	Patient levy		12.36 ± 45.28	261,028,782.73		Patient levy			138.47 ± 866.29	391,744.41	
2007	Total cost	19,075,724	100.56 ± 324.11	1,918,284,176.66	***2007***	Total cost	3,595	0.019	8633.78 ± 3821.67	31,038,438.00	1.62
	Scheme amount		84.66 ± 304.10	1,615,007,032.92		Scheme amount			8400.62 ± 3998.51	30,200,226.57	
	Patient levy		15.90 ± 101.24	303,277,143.74		Patient levy			233.16 ± 1411.16	838,211.43	
2008	Total cost	16,439,253	108.63 ± 436.75	1,785,871,013.85	***2008***	Total cost	3,731	0.023	9586.25 ± 5956.56	35,766,286.42	2.00
	Scheme amount		89.94 ± 419.97	1,478,548,228.92		Scheme amount			9400.26 ± 6052.02	35,072,366.57	
	Patient levy		18.69 ± 107.16	307,322,784.93		Patient levy			185.99 ± 1218.94	693,919.85	

% n = $n_{\text{biologic immunomodulators}}$ / $n_{\text{total database}}$ x 100

% R = total $\text{cost}_{\text{biologic immunomodulators}}$ / total $\text{cost}_{\text{total database}}$ x 100

Based on Table 4.4.2 and Figure 4.5, the average cost per biologic immunomodulating medicine item was significantly (approximately 60 times) higher than the average cost per medicine item on the total database for each year between 2005 and 2008 (*d*-values = 2.54 in 2005; 3.32 in 2006; 2.23 in 2007 and 1.59 in 2008). The average cost per biologic immunomodulator furthermore increased with 71.10% during the four-year study period. The average scheme amount for a biologic immunomodulator increased with 74.13% between 2005 and 2008, whereas the average patient levy for these medicine items decreased with 9.82% between 2005 and 2008 (refer to Table 4.4.2).

Table 4.4.2 furthermore shows that only 0.009% (n = 1,759) of the total number of medicine items that were claimed in 2005 were biologic immunomodulators, whereas in 2006, an indicated 0.013% (n = 2,829) of all the medicine items claimed through the PBM were biologic immunomodulators. In 2007, 0.019% (n = 3,595) of the total number of medicine items on the database were biologic immunomodulators, and in 2008, 0.023% (n = 3,731) of the total number of medicine items that were claimed were biologic immunomodulators, which means that from 2005 to 2008, the percentage medicine items on the total database represented by biologic immunomodulators increased with 0.014%.

Figure 4.6 indicates what percentage of all the biologic immunomodulators that were prescribed during 2005 and during 2008 was represented by the different immunomodulators.

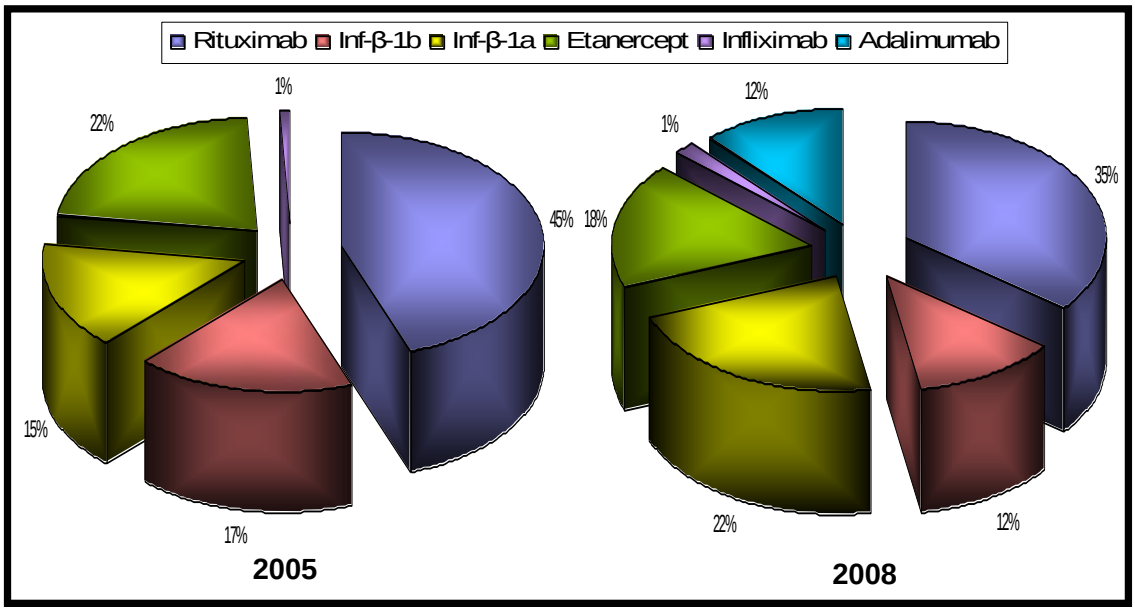

Figure 4.6 Percentage of biologic immunomodulators represented by each individual biological medicine item

Figure 4.6 shows that rituximab represented almost half of all the biologic immunomodulators prescribed in 2005, followed by etanercept. Infliximab represented the smallest percentage of all the biologic immunomodulators, whereas adalimumab had not been prescribed at all during 2005. In 2008, the percentage of all the biologic immunomodulators represented by rituximab was smaller, but still more than two thirds of all the biologic immunomodulators prescribed that year. The percentage of the total number of biologic immunomodulators claimed in 2008 represented by infliximab almost doubled since 2005, but it was still the smallest. Adalimumab represented 11% of all the biologic immunomodulators claimed in 2008, and interferon beta-1a, which represented the second smallest percentage of the total biologic immunomodulators in 2005, represented the second largest percentage in 2008.

Table 4.4.3 shows the frequencies at which all six the individual biologic immunomodulators were claimed during the four years. The frequencies with at these biologics were claimed include all the claims made for any one of the six biologic immunomodulators relevant to this study between 2005 and 2008, and not necessarily only those claimed by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease.

Table 4.4.3 shows that the frequencies at which all six biologic immunomodulators were prescribed each year increased between 2005 and 2008, and that rituximab was claimed the most, whereas infliximab was claimed the least every year.

The frequencies at which adalimumab and interferon beta-1a were prescribed thus increased significantly between 2005 and 2008. Infliximab was also prescribed at a slightly higher frequency each year, whereas the frequencies at which rituximab and interferon beta-1b were prescribed steadily decreased over the four years (refer to Figure 4.6 and Table 4.4.3).

Table 4.4.3 Frequencies of biologic immunomodulators per year (Snyman, 2010)

Year	Pharmacological code (MIMS)	Active ingredient name	Trade name	Frequency
2005	12.10.1	Infliximab	Revellex® 100mg/10ml	14
	23.1.1	Rituximab	Mabthera® 500mg	430
	23.1.1	Rituximab	Mabthera® 100mg	354
	24.2.1	Interferon beta-1b	Betaferon®	307
	24.2.1	Interferon beta-1a	Rebif® 44mcg/0.5ml	136
	24.2.1	Interferon beta-1a	Avonex® 30mcg	97
	24.2.1	Interferon beta-1a	Rebif® 22mcg/0.5ml	35
	4.6.1	Etanercept	Enbrel® 25mg	386
2006	12.10.1	Infliximab	Revellex® 100mg/10ml	24
	23.1.1	Rituximab	Mabthera® 500mg	676
	23.1.1	Rituximab	Mabthera® 100mg	597
	24.1.1	Adalimumab	Humira® 40mg/0.8ml	88
	24.2.1	Interferon beta-1b	Betaferon®	429
	24.2.1	Interferon beta-1a	Rebif® 44mcg/0.5ml	268
	24.2.1	Interferon beta-1a	Avonex® 30mcg	256
	24.2.1	Interferon beta-1a	Rebif® 22mcg/0.5ml	73
	4.6.1	Etanercept	Enbrel® 25mg	418
2007	12.10.1	Infliximab	Revellex® 100mg/10ml	33
	23.1.1	Rituximab	Mabthera® 100mg	716
	23.1.1	Rituximab	Mabthera® 500mg	688
	24.1.1	Adalimumab	Humira® 40mg/0.8ml	319
	24.2.1	Interferon beta-1b	Betaferon®	464
	24.2.1	Interferon beta-1a	Rebif® 44mcg/0.5ml	374
	24.2.1	Interferon beta-1a	Avonex® 30mcg	367
	24.2.1	Interferon beta-1a	Rebif® 22mcg/0.5ml	51
	4.6.1	Etanercept	Enbrel® 25mg	583
2008	12.10.1	Infliximab	Revellex® 100mg/10ml	55
	23.1.1	Rituximab	Mabthera® 500mg	666
	23.1.1	Rituximab	Mabthera® 100mg	657
	24.1.1	Adalimumab	Humira® 40mg/0.8ml	438
	24.2.1	Interferon beta-1b	Betaferon®	443
	24.2.1	Interferon beta-1a	Rebif® 44mcg/0.5ml	402
	24.2.1	Interferon beta-1a	Avonex® 30mcg	375
	24.2.1	Interferon beta-1a	Rebif® 22mcg/0.5ml	35
	4.6.1	Etanercept	Enbrel® 25mg	660

4.3.1.3 Number of prescriptions and average cost per prescription

Table 4.4.4 summarises the annual frequencies and average costs of those prescriptions that contained any one of the six biologic immunomodulating medicine items between 2005 and 2008, and compares it to the frequencies and average prescription costs of all prescriptions on the total database for the same period.

According to Table 4.4.4, 0.016% (n = 1,319) of the total number of prescriptions claimed through the PBM during 2005 were for biologic immunomodulators, whereas 0.023% (n = 2,056) of the total number of prescriptions that were claimed in 2006 contained biological medicine items. The percentage prescriptions that contained biologic immunomodulators further increased to 0.038% (n = 2,971) in 2007 and to 0.047% (n = 3,193) in 2008 (refer to Table 4.4.4). The percentage prescriptions for biologic immunomodulators thus increased each year, culminating a 0.031% increase in the number of prescriptions claimed for these items over the four-year study period (refer to Table 4.4.4).

Table 4.4.4 Number of prescriptions and average cost per prescription: total database *vs* target population

AVERAGE COST PER PRESCRIPTION FOR TOTAL DATABASE					AVERAGE COST PER PRESCRIPTION FOR BIOLOGIC IMMUNOMODULATORS						
Year	**Variable**	**Frequency (n = Prescriptions)**	**Mean ± SD (R)**	**Total cost (R)**	**Year**	**Variable**	**Frequency (n = Prescriptions)**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**% R**
2005	Total cost	8,391,836	216.86 ± 342.30	1,819,865,251.63	***2005***	Total cost	1,319	0.016	7471.69 ± 4489.77	9,855,161.01	0.54
	Scheme amount		190.95 ± 323.66	1,602,447,649.43		Scheme amount			7199.28 ± 4604.33	9,495,851.34	
	Patient levy		25.91 ± 81.07	217,417,602.20		Patient levy			272.41 ± 1251.63	359,309.67	
2006	Total cost	8,906,348	220.04 ± 395.22	1,959,738,734.09	***2006***	Total cost	2,054	0.023	9226.47 ± 4959.61	18,951,176.69	0.97
	Scheme amount		190.73 ± 377.73	1,698,709,951.36		Scheme amount			9035.75 ± 5093.86	18,559,432.28	
	Patient levy		29.31 ± 88.47	261,028,782.73		Patient levy			190.72 ± 1053.75	391,744.41	
2007	Total cost	7,911,096	242.48 ± 600.31	1,918,284,176.66	***2007***	Total cost	2,971	0.038	10447.13 ± 6337.29	31,038,438.00	1.62
	Scheme amount		204.14 ± 564.37	1,615,007,032.92		Scheme amount			10165.00 ± 6457.94	30,200,226.57	
	Patient levy		38.34 ± 171.45	303,277,143.74		Patient levy			282.13 ± 1734.71	838,211.43	
2008	Total cost	6,775,873	263.56 ± 789.01	1,785,871,013.85	***2008***	Total cost	3,193	0.047	11201.47 ± 8890.93	35,766,286.42	2.00
	Scheme amount		218.21 ± 756.95	1,478,548,228.92		Scheme amount			10984.14 ± 8936.03	35,072,366.57	
	Patient levy		45.36 ± 181.31	307,322,784.93		Patient levy			217.33 ± 1424.89	693,919.85	

% Rx = $n_{\text{biologic immunomodulators}}$ / $n_{\text{total database}}$ x 100

% R = total $\text{cost}_{\text{biologic immunomodulators}}$ / total $\text{cost}_{\text{total database}}$ x 100

Based on Table 4.4.4, Figure 4.7 shows what portion of the total number of prescriptions claimed each year between 2005 and 2008 was represented by prescriptions that contained biologic immunomodulating medicine items.

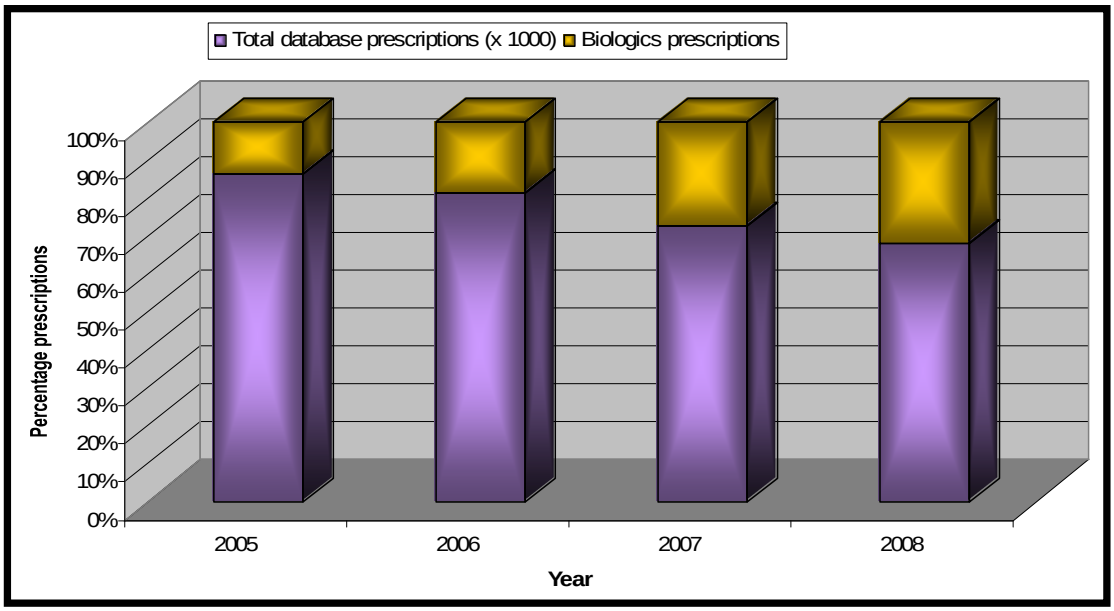

Figure 4.7 Portion of the total number of prescriptions on the database that contained biological medicine items between 2005 and 2008

Based on Table 4.4.4, the average cost per prescription that contained a biologic immunomodulator between 2005 and 2008, was noticeably higher than the average cost per prescription on the total database. The *d*-values indicate that the difference in the average prescription cost of a prescription that contained a biologic immunomodulator and a prescription on the total database was practically significant (*d*-values = 1.62 for 2005; 1.82 for 2006; 1.61 for 2007; 1.23 for 2008).

Table 4.4.4 further indicates that the average cost per prescription with a biological medicine item increased each year between 2005 and 2008, along with the increase in the average cost per prescription on the total database. From 2005 to 2008 there was a 49.92% increase in the average cost of a prescription that contained a biologic immunomodulator. The average scheme amount increased with 52.57% from 2005 to 2008, whereas the average patient levy decreased with 25.34%.

4.3.1.4 Total annual medicine expenditure and the contribution of the medical aid scheme and the patient to the total medication cost

According to Tables 4.4.2 and 4.4.4, biologics contributed 0.54% (R9, 855,161.01) of the total medicine expenditure for 2005, compared to the 0.97% (R18, 951,176.69) these medicine items contributed to the total medication cost in 2006. In 2007, biologics contributed 1.62% (R31, 038,438.00) of the total medication cost for that year, which was almost double the percentage of 2006. The amount spent on biologic immunomodulators in 2008 contributed 2.00% (R35, 766,286.42) of the total medicine expenditure for that year. Thus, from 2005 to 2008 the percentage of the total medicine expenditure spent on biologic immunomodulators increased with 1.46%. Figure 4.8 illustrates the contribution of biologics prescriptions to the total cost of all the medication claimed through the PBM each year between 2005 and 2008.

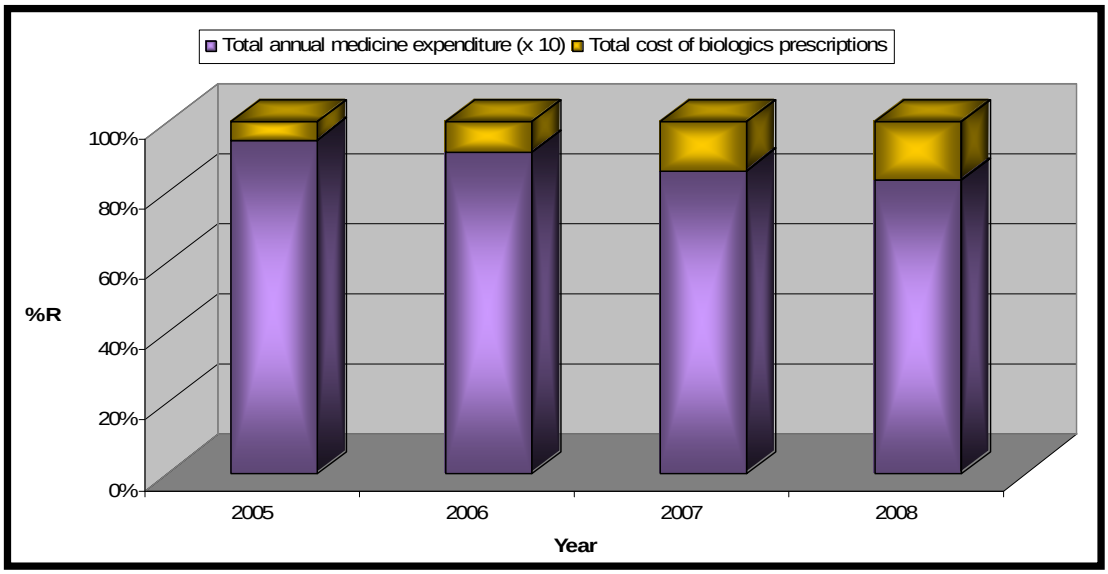

Figure 4.8 Contribution of biologic immunomodulators to total annual medicine expenditure

Based on Tables 4.4.2 and 4.4.4, the medical aid scheme's contribution to the total cost of biologic immunomodulating medicine was 96.35% in 2005, whereas the patient's contribution was only 3.65% (refer to Table A.13 in appendix B). In 2008 the medical aid scheme paid 98.06% of the total medicine expenditure and the patient co-paid only 1.94%. The medical aid scheme's contribution to the final medication cost of biologic immunomodulators thus increased with 1.71% from 2005 to 2008 (refer to Table A.13 in appendix B).

On the other hand, the medical aid scheme paid 88.05% of the total medication cost of all the medication claimed through the PBM during 2005, and the patient paid the remaining 11.95% (refer to Table A.1 in appendix B), which was 8% more than the patient levy for a

biologic immunomodulator, and in 2008, the medical aid scheme's contribution to the total cost of all the medication claimed through the PBM was 5.26% less than in 2005, since the medical scheme paid 82.79% of the total medication cost and the patient paid the remaining 17.21% (refer to Table A.1 in appendix B). The medical aid scheme's contribution to the total medication cost of biologic immunomodulators thus increased between 2005 and 2008, whereas its contribution to the total cost of all the medication on the total database (both biologics and other medication) decreased (refer to Tables A.1 and A.13 in appendix B).

Figure 4.9 illustrates how the contribution of the medical aid scheme and the patient to the total medicine expenditure for the total database compared to the contribution of the medical aid scheme and the patient to the total medication cost of the target population between 2005 and 2008.

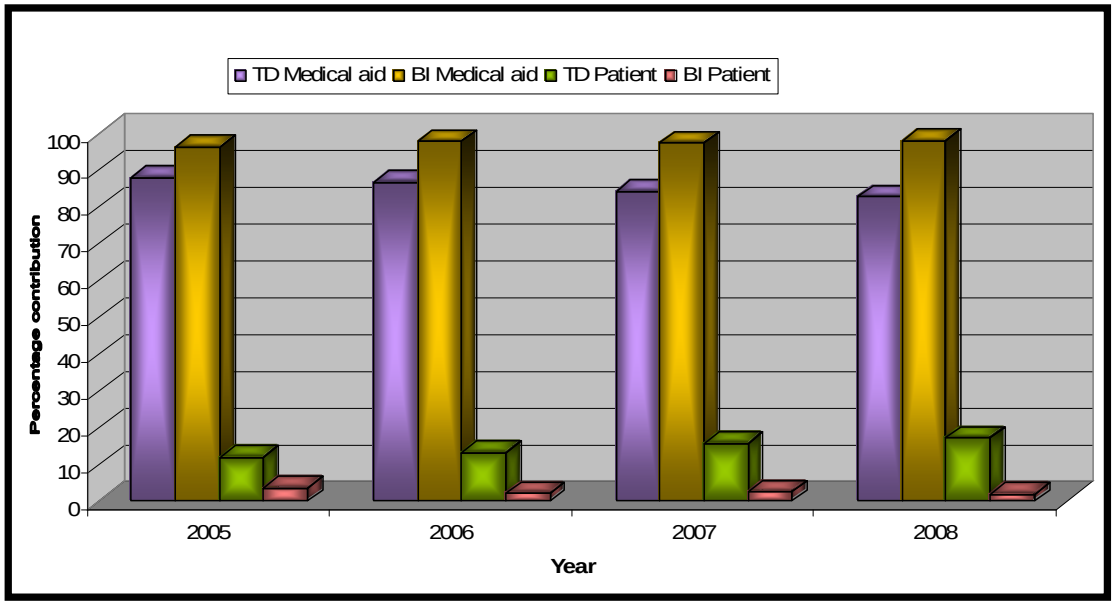

Figure 4.9 Contributions of the medical aid scheme and the patient to the total medication cost for the total database (TD) and the total cost of biologic immunomodulators (BI)

4.3.1.5 Summary of analysis of target population

From the analysis done above, it is clear that both the frequency with which biologic immunomodulators were claimed, as well as their contribution to the total annual medicine expenditure of the database increased between 1 January 2005 and 31 December 2008. The percentage prescriptions for biologic immunomodulators increased with 0.031% between 2005 and 2008, whereas the percentage that biologic immunomodulators contributed to the total medication cost increased with 1.46% from 2005 to 2008. This may seem like a small increases, but based on Tables 4.4.2 and 4.4.4, the percentage that biologic immunomodulators contributed to the total annual medicine expenditure almost doubled each year between 2005 and 2008 (refer to Tables 4.4.2 and 4.4.4).

Because not only the cost percentage, but also the frequency of claims for biologic immunomodulators increased, an accurate conclusion cannot be drawn from only the percentage values as to whether the cost percentage increased because of the increased prevalence, or because biological medicine items actually became more expensive each year. Furthermore, because the number of patients who claimed biologics through the PBM also increased between 2005 and 2008 (a net increase of 0.024% from 2005 to 2008) (refer to Table 4.4.1), it can be argued that the increase in the number of claims for biologics was due to an increase in the number of patients who claimed these agents [whether because of increases in disease prevalence or because of changes in the mix of patients on the database (refer to section 4.2.1)], which could also cause an increase in the medicine expenditure.

However, from the analysis it is evident that the average cost per biologic immunomodulating medicine item did increase every year, as the average cost per biologic immunomodulating medicine item increased with 71.10% between 2005 and 2008. The average cost per prescription that contained a biologic immunomodulator also increased with 49.92% from 2005 to 2008. These percentage values calculated for the average cost per prescription indicate that, together with an increased prevalence of use, biologic immunomodulators also became more expensive each year (refer to Table 4.4.2 and Table 4.4.4).

This, however, does not indicate how the cost and the prevalence of these medicine items correlate. From Table 4.4.4 it is clear that prescriptions that contained biologic immunomodulators only represented a very small percentage of the total number of prescriptions claimed per year, and even though the cost percentage of these prescriptions was slightly higher than the frequency percentage, biologic immunomodulators also only contributed to a very small percentage of the total medicine expenditure of each year.

Since both the cost and frequency percentages are so small, it is difficult to conclude from only percentage values whether the costs of these items are in line with their prevalence on the database. It is, however, possible to determine the ratio between the cost and the prevalence of biologic medicine by calculating the CPI (cost prevalence index) of the biologic immunomodulators, by means of dividing the cost percentage (% R) by the frequency percentage (% n). As stated in section 3.4.3.3, a CPI greater than 1 is an indication that the treatment is relatively expensive.

The CPI for biologic immunomodulators was determined for those prescriptions that contained biologic immunomodulators each year. The CPI was 33.75 for 2005; 42.17 for 2006; 42.63 for 2007; and 42.55 for 2008. As all these values are significantly greater than 1, it can be accurately concluded that biologic immunomodulating medicines are relatively expensive.

Yet, even though it is clear that biologic immunomodulating medicines are relatively expensive, the percentage contributed by biologics to the total annual medicine expenditure seems relatively small and insignificant. But when the average cost per prescription for a biologic medicine item is compared to the average cost per prescription for a prescription on the total database, the significance of the cost impact of these items is indicated.

Not only is it evident from Tables 4.4.2 and 4.4.4 that the average cost per biologic immunomodulator was almost 60 times higher than the average cost of medicine items on the total database, but also that the cost of a biologic prescriptions was almost 50 times as much as the average cost per prescription without a biologic. However, from the *d*-values, or effect-sizes (refer to chapter 3) the significance of the cost impact of treatment with biologics is indicated.

The *d*-value for a biologic immunomodulator was 2.54 in 2005, 3.32 in 2006, 2.23 in 2007 and 1.59 in 2008. The *d*-value for prescriptions that contained a biologic immunomodulator in 2005 was 1.62 and in 2006 it was 1.82, whereas in 2007 the *d*-value was 1.61 in and 1.23 in 2008. According to the guidelines given by Steyn (1998:3) (refer to paragraph 3.4.3.4), the effect of a treatment is considered to be large and significant, and of practical importance when $d \geq 0.8$. Since the *d*-values for biologic immunomodulators were greater than 0.8 each year, the size of biologics' effect can be considered to be large and practically significant.

4.3.2 Analysis of the target population according to gender

As discussed in section 4.2.2.1.3, the patient population of the database is not evenly distributed between males and females. Table 4.1.2 showed that the male population represented approximately 44% of the total patient population each year, whereas females represented approximately 55% of the total patient population every year during the four-year study period.

However, since the patient population of the database is the total population of the PBM database and not a random sampling out of a population, the inequity does not cause bias. Every patient in the database had an equal chance of being diagnosed with the autoimmune conditions relevant to this study. The total database was screened and all patients with a positive ICD-10 or claim code were selected to be part of the study population. Therefore, comparisons can be made between the male and female population of the total database and the target population and accurate conclusions can be drawn.

4.3.2.1 Number of patients and average number of prescriptions per patient per year according to gender

Table 4.4.5 compares the gender distribution of the patient population of the total database with the gender distribution of the target population over the four-year study period.

Table 4.4.1 showed that there were 198 patients who received biologics in 2005 (refer to section 4.3.1.1). Based on Table 4.4.5, 69.19% (n = 137) of these patients were female and 30.81% (n = 61) were male. In 2006, a total of 279 patients received biologics, of whom 68.82% (n = 192) were female and 31.17% (n = 87) were male, and in 2007, 64.78% (n = 241) of all the patients who received biologics (n = 372) were female, whereas 35.22% (n = 131) were male. In 2008, female patients who received biologics represented 63.22% (n = 263) of the total number of patients (n = 416) who received biologics that year, and male patients represented the remaining 36.78% (n = 153). Thus, out of all the patients who received biologics during the four years, approximately two thirds were female and one third were male.

Table 4.4.5 Number of patients and average number of prescriptions per patient per year according to gender

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT FOR TOTAL DATABASE					AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT FOR BIOLOGIC IMMUNOMODULATORS						
Year	Gender	Frequency (n = Patients)	Total number of prescriptions	Average Rx per patient Mean ± SD	Year	Gender	Frequency (n = Patients)	% of total number of biologics users	% of total number of males / females on total database	Total number of prescriptions	Average Rx per patient Mean ± SD
2005	F	842,386	5,036,494	5.98 ± 7.16	*2005*	F	137	69.19	0.016	950	6.03 ± 4.94
	M	665,505	3,348,219	5.03 ± 6.15		M	61	30.81	0.009	369	6.05 ± 5.10
	U	1,730	7,123	4.12 ± 5.21		U	0	0.00	0.00	0	-
2006	F	868,891	5,336,202	6.14 ± 7.37	*2006*	F	192	68.82	0.022	1,479	7.70 ± 4.70
	M	688,091	3,565,328	5.18 ± 6.35		M	87	31.17	0.013	575	6.61 ± 4.02
	U	1,108	4,814	4.34 ± 5.78		U	0	0.00	0.00	0	-
2007	F	654,348	4,754,911	7.27 ± 7.99	*2007*	F	241	64.78	0.037	2.008	8.33 ± 4.49
	M	523,841	3,154,355	6.02 ± 6.90		M	131	35.22	0.025	963	7.35 ± 4.34
	U	407	1,818	4.47 ± 5.20		U	0	0.00	0.00	0	-
2008	F	538,254	4,062,385	7.55 ± 8.32	*2008*	F	263	63.22	0.049	2,133	8.11 ± 4.86
	M	436,243	2,713,478	6.22 ± 7.15		M	153	36.78	0.035	1,060	6.93 ± 4.55
	U	-	-	-		U	0	0.00	0.00	0	-

F = female; M = male; U = unidentified.

% of total number of biologics users = n_{gender} / (n_{female} + n_{males} for biologic immunomodulators) x 100

% of total number of males or females on total database = $n_{biologic\ immunomodulators}$ / $n_{total\ database}$ x 100

Based on Table 4.4.5, female patients who received biologics in 2005 represented 0.009% of the total patient population of the database whereas male patients who received biologics represented 0.004% of the total patient population of the database. In 2006, females who received biologics represented 0.012% of the total patient population, whereas males who received biologics represented 0.006% of the total patient population. Female patients who received biologics in 2007 represented 0.020% of the total patient population, whereas males who received biologics represented 0.011% of the total patient population of the database. The percentage males and females of the total database represented by biologics users increased further between 2007 and 2008, as 0.026% of the total patient population of the database in 2008 was represented by female patients who received biologics, and 0.016% was represented by male patients who received biologics. Thus, female patients who received biological medicine items between 2005 and 2008 represented a larger percentage of the total patient population of the database than male patients who received such medicine items.

When the percentage male and female patients who received biologic immunomodulators between 2005 and 2008 is calculated as a percentage of the total number of male and female patients on the total database, Table 4.4.5 shows that out of the total number of female patients, 137 (0.016%) received biologic immunomodulators in 2005, and 0.009% (n = 61) of the total number of male patients received biologics in the same year. In 2006, 0.022% (n = 192) of all the females and 0.013% (n = 87) of all the males on the database received biologics, whereas in 2007, female patients who received biologics represented 0.037% (n = 241) of the total female population of the database, and male patients who received biologics represented 0.025% (n = 131) of the total male population of the database. In 2008, 0.049% (n = 263) of all the female patients and 0.035% (n = 153) of all the male patients on the database received biologics.

Figure 4.10.1 illustrates how the number of female and male patients who received biologics each year compared. Figure 4.10.1 illustrates what portion of the total number of male and female patients on the database was represented by patients who received biologics.

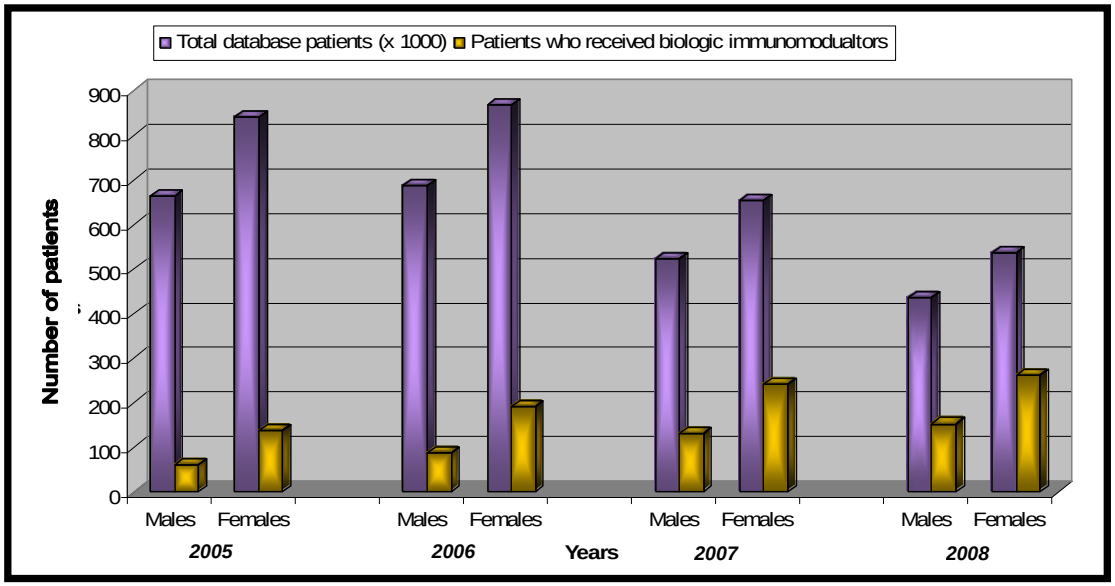

Figure 4.10.1 Number of males and females who received biologics each year compared to the total number of males and females on the database

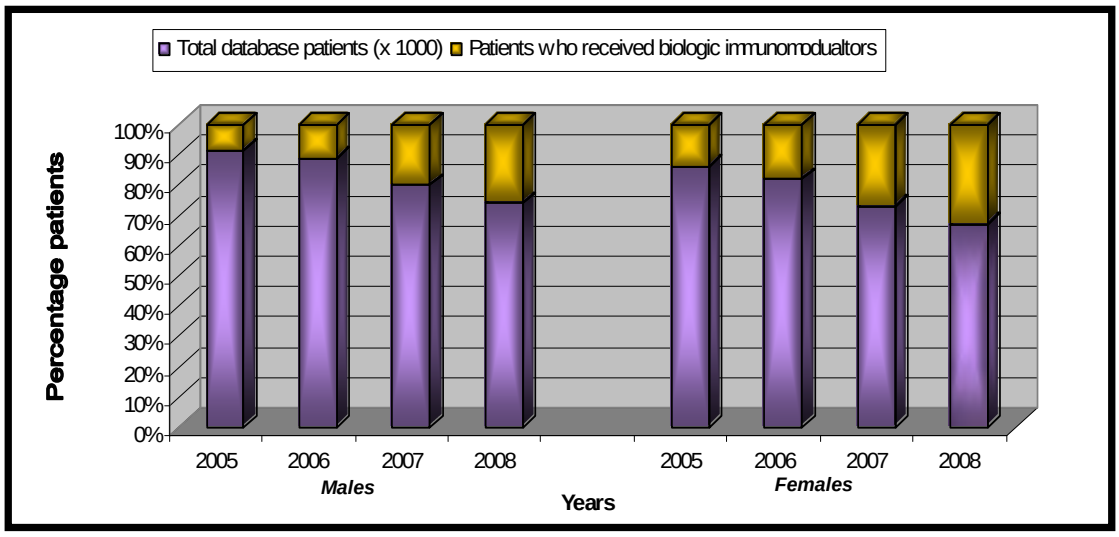

Figure 4.10.2 Percentage males and females who received biologics each year

According to Table 4.4.5, female patients on the total database received on average between 5.98 ± 7.16 (2005) and 7.55 ± 8.32 (2008) prescriptions per year, whereas female patients receiving prescriptions for biologic immunomodulators received an average of between 6.03 ± 4.94 (2005) and 8.11 ± 4.86 (2008) prescriptions per year during the study period. On the other hand, male patients on the total database received on average between 5.03 ± 6.15 (2005) and 6.22 ± 7.15 (2008) prescriptions per year, whereas male patients who received biologics received an average of between 6.05 ± 5.10 (2005) and 6.93 ± 4.55 (2008) prescriptions per year.

The *d*-values indicate that there was not a big difference in the average number of prescriptions per patient per year between the total database and the target population (*d*-values for females = 0.007 in 2005; 0.21 in 2006; 0.13 in 2007 and 0.07 in 2008; and *d*-values for males = 0.17 in 2005; 0.23 in 2006; 0.19 in 2007 and 0.1 in 2008).

4.3.2.2 Number of prescriptions and average cost per prescription according to gender

Table 4.4.6 summarises the frequencies and average costs of prescriptions that contained any one of the six biologic immunomodulating medicines between 2005 and 2008 according to gender.

According to Table 4.4.6, in 2005 and 2006 approximately 72% of all the prescriptions that contained biologic immunomodulators were claimed for female patients and approximately 28% were claimed for male patients. In 2007, prescriptions that contained biologic immunomodulators claimed for female patients represented only 67.59% of the total number of prescriptions that contained biologics, and in 2008, 66.80% of the total number of prescriptions that contained biologic immunomodulators had been claimed for female patients.

This indicates that more than two thirds of all the prescriptions that contained biologic immunomodulators between 2005 and 2008 were claimed for female patients, but that the percentage of the prescriptions that contained biological medicine items represented by female patients decreased between 2005 and 2008 (see Figure 4.11).

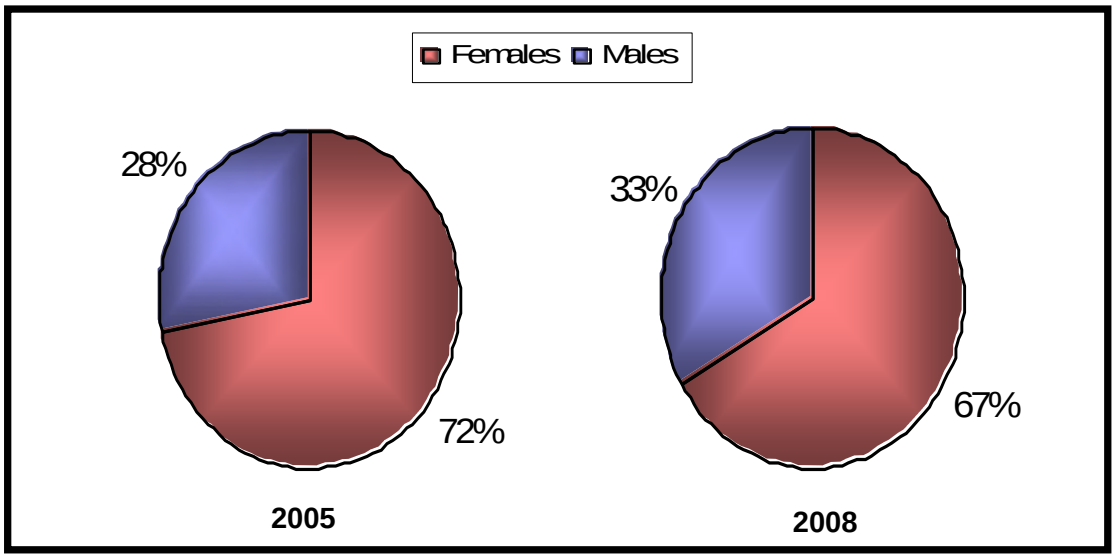

Figure 4.11 Percentage of all the prescriptions on the database that contained biologic immunomodulators according to gender

Table 4.4.6 Number of prescriptions and average cost per prescription according to gender

AVERAGE COST PER PRESCRIPTION ACCORDING TO GENDER FOR TOTAL DATABASE						AVERAGE COST PER PRESCRIPTION ACCORDING TO GENDER FOR BIOLOGIC IMMUNOMODULATORS							
Year	Gender	Variable	Frequency (n = Prescriptions)	Mean ± SD (R)	Total cost (R)	Year	Gender	Variable	Frequency (n = Prescriptions)	% Rx	Mean ± SD (R)	Total cost (R)	% R
2005	F	Total cost	5,036,494	215.35 ± 330.75	1819,865,251.63	2005	F	Total cost	950	0.019	7049.03 ± 3817.07	6,696,578.10	0.368
		Scheme amount		188.16 ± 310.90	947,688,793.44			Scheme amount			6798.55 ± 3979.38	6,458,625.72	
		Patient levy		27.19 ± 80.87	136,938,071.85			Patient levy			250.48 ± 1125.06	237,952.38	
	M	Total cost	3,348,219	219.15 ± 358.17	733,769,633.85		M	Total cost	369	0.011	8559.85 ± 5742.37	3,158,582.91	0.430
		Scheme amount		195.14 ± 341.05	653,370,941.06			Scheme amount			8230.96 ± 5797.35	3,037,225.62	
		Patient levy		24.01 ± 81.38	80,398,692.79			Patient levy			328.88 ± 1530.42	121,357.29	
	U	Total cost	7,123	206.20 ± 622.31	1,468,752.49		U	Total cost	0	0	-	0.00	0
		Scheme amount		194.85 ± 615.57	1,387,914.93			Scheme amount			-	0.00	
		Patient levy		11.35 ± 41.06	80,837.56			Patient levy			-	0.00	
2006	F	Total cost	5,336,203	217.81 ± 380.43	1162,254,536.29	2006	F	Total cost	1,479	0.028	8392.75 ± 3497.26	12,412,874.96	1.068
		Scheme amount		187.21 ± 361.56	999,015,475.00			Scheme amount			8180.89 ± 3658.27	12,099,541.59	
		Patient levy		30.59 ± 89.95	163,239,061.29			Patient levy			211.85 ± 1066.59	313,333.37	
	M	Total cost	3,565,331	223.36 ± 416.16	796,360,401.04		M	Total cost	575	0.016	11370.96 ± 7077.18	6,538,301.73	0.821
		Scheme amount		195.97 ± 400.43	698,682,181.29			Scheme amount			11234.59 ± 7184.61	6,459,890.69	
		Patient levy		27.40 ± 86.20	97,678,219.75			Patient levy			136.37 ± 1018.87	78,411.04	
	U	Total cost	4,814	233.44 ± 529.46	1,123,796.76		U	Total cost	0	0	-	0.00	0
		Scheme amount		210.28 ± 524.10	1,012,295.07			Scheme amount			-	0.00	
		Patient levy		23.16 ± 59.04	111,501.69			Patient levy			-	0.00	
	F	Total cost	4,754,911	239.37 ± 559.98	1138,188,990.86		F	Total cost	2,008	0.042	9517.42 ± 5415.84	19,110,975.64	1.679
		Scheme amount		199.59 ± 530.41	949,029,333.61			Scheme amount			9292.93 ± 5478.63	18,660,195.15	
		Patient levy		39.78 ± 148.33	189,159,657.25			Patient levy			224.49 ± 1499.42	450,780.49	
	M	Total cost	3,154,367	247.12 ± 656.34	779,508,488.81		M	Total cost	963	0.031	12385.73 ± 7565.11	11,927,462.36	1.530
		Scheme amount		210.97 ± 611.87	665,466,500.10			Scheme amount			11983.42 ± 7825.49	11,540,031.42	

Table 4.4.6 Number of prescriptions and average cost per prescription according to gender *(continued)*

2007		Patient levy		36.15 ± 201.38	114,041,988.71	***2007***		Patient levy			402.32 ± 2139.73	387,430.94	
	U	Total cost	1,818	322.72 ± 697.81	586,696.99		**U**	Total cost	0	0	-	0.00	0
		Scheme amount		281.19 ± 688.75	511,199.21			Scheme amount			-	0.00	
		Patient levy		41.53 ± 53.27	75,497.78			Patient levy			-	0.00	
	F	Total cost	4,062,385	260.26 ± 752.96	1057,274,453.63		**F**	Total cost	2,133	0.053	10194.35 ± 7836.56	21,744,544.89	2.057
		Scheme amount		213.17 ± 716.56	865,959,792.23			Scheme amount			9997.24 ± 7895.03	21,324,107.35	
		Patient levy		47.09 ± 195.17	191,314,661.40			Patient levy			197.11 ± 1257.95	420,437.54	
	M	Total cost	2,713,488	268.51 ± 840.07	728,596,560.22		**M**	Total cost	1,060	0.039	13228.06 ± 10415.18	14,021,741.53	1.924
		Scheme amount		225.76 ± 813.62	612,588,436.69			Scheme amount			12970.06 ± 10454.30	13,748,259.22	
2008		Patient levy		*42.75 ± 158.27*	116,008,123.53	***2008***		Patient levy			258.00 ± 1712.14	273,482.31	
	U	Total cost	0	-	0.00		**U**	Total cost	0	0	-	0.00	0
		Scheme amount		-	0.00			Scheme amount			-	0.00	
		Patient levy		-	0.00			Patient levy			-	0.00	

F = Female; M = Male; U = Unidentified.

% Rx = $n_{\text{biologic immunomodulators}}$ / $n_{\text{total database}}$ x 100

% R = total $\text{cost}_{\text{biologic immunomodulators}}$ / total $\text{cost}_{\text{total database}}$ x 100

Calculated as a percentage of the total number of prescriptions claimed for each gender group per year, the percentage prescriptions that contained biologic immunomodulators every year was as follows: in 2005, 0.019% (n = 950) of the total number of prescriptions claimed for female patients on the total database contained biologic immunomodulators, and 0.011% (n = 369) of the total number of prescriptions claimed for male patients on the total database contained biologic immunomodulators. In 2006, 0.028% (n = 1,479) of the total number of prescriptions claimed for the female population of the database contained biologic immunomodulators, whereas 0.016% (n = 575) of the total number of prescriptions claimed for the male population contained biologic immunomodulators. In 2007, 0.042% (n = 2,008) of all the prescriptions claimed for females and 0.031% (n = 963) of all the prescriptions claimed for males contained biologic immunomodulators, and in 2008, 0.053% of all the prescriptions claimed for females and 0.039% of all the prescriptions claimed for males contained biologic immunomodulators (refer to Table 4.4.6).

The percentage prescriptions for biologics claimed for female patients through the PBM thus increased with 0.034% from 2005 to 2008, and the percentage prescriptions for biologics claimed for male patients increased with 0.028% during the same period. Thus, even though there was an increase in the percentage prescriptions for biologic immunomodulators claimed for both male and female patients each year, there were more prescriptions for biologics claimed for females than for males (refer to Table 4.4.6). Figure 2.12 illustrates what portion of the total number of prescriptions claimed for males and females was represented by biologic immunomodulators.

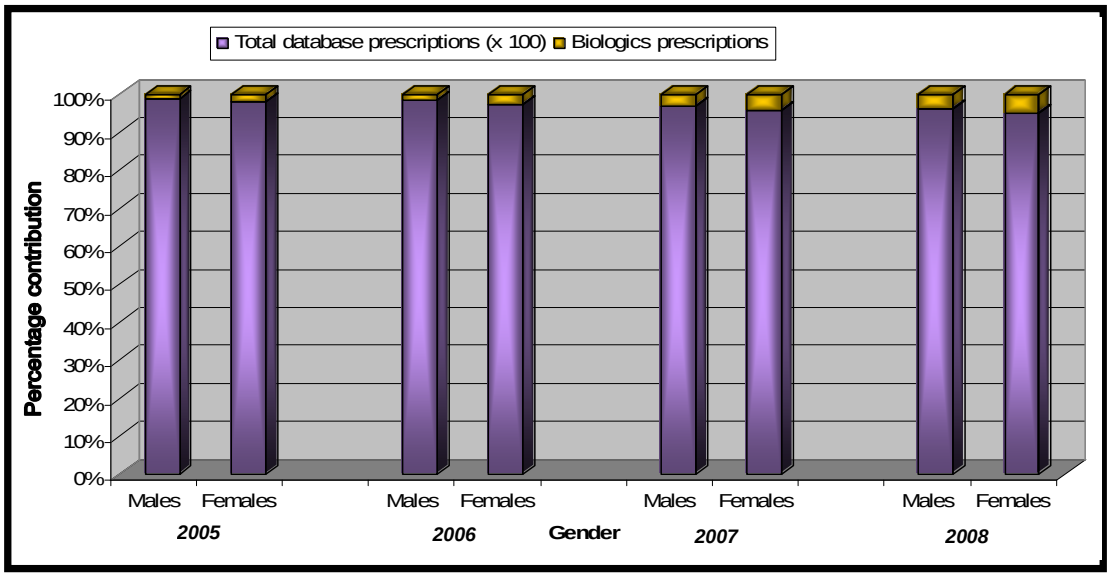

Figure 4.12 Prescriptions that contained biologic immunomodulators as a portion of the total number of prescriptions claimed for male and female patients each year

Table 4.4.6 furthermore shows the average cost per prescription for males and females, and when the average cost per prescription between the two genders is compared, it is indicated that the average cost per prescription that contained a biologic immunomodulator was higher for a male patient than for a female patient. The average cost per prescription that contained a biological medicine item was on average 30% more for a male patient than the average cost per prescription that contained a biological medicine items for a female patient. Figure 4.13 illustrates the difference in the average cost per biologics prescription between males and females.

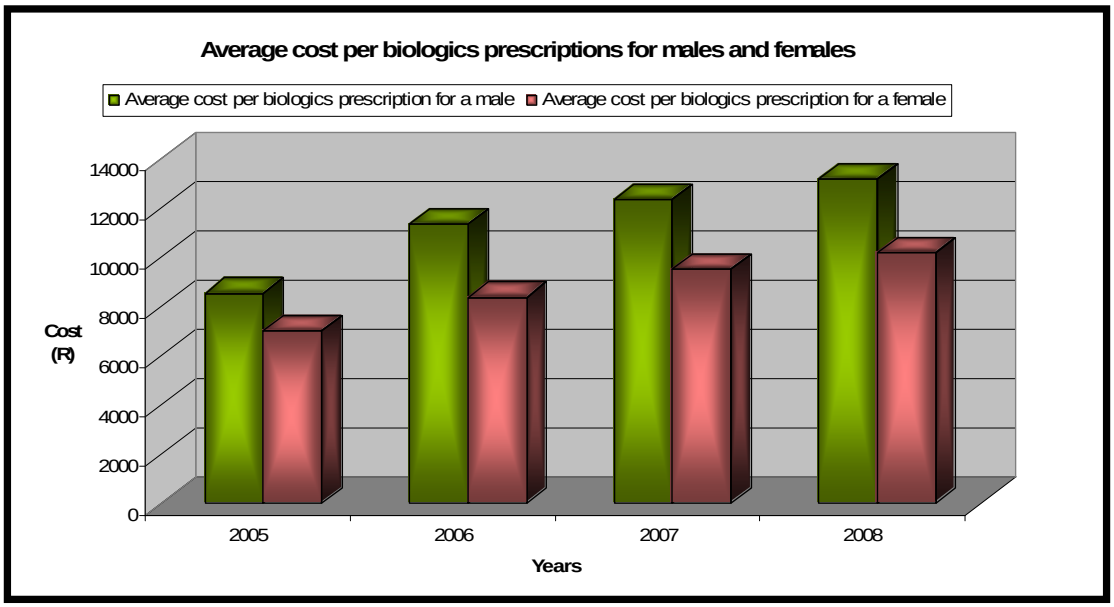

Figure 4.13 Average cost per biologic prescription for a male patient *vs* average cost per biologic prescription for a female patient between 2005 and 2008

Furthermore, the average cost per prescription for a male patient who received biologics increased with 54.54% between 2005 and 2008, whereas the average cost per prescription for a female patient who received biologics increased with only 44.62% during the same time. The average patient levy for a prescription that contained biological medicine items decreased with 53.37% for a male patient, but with only 27.47% for a female patient (refer to Table 4.4.6). The reason for the larger decrease in the average patient levy for males than for females may be ascribed to the fact that the average cost of prescriptions that contained biologic immunomodulators was higher for males than for females, but the percentage contribution of the medical aid scheme to the total prescription cost is relatively the same for both genders (refer to Tables A.14 and A.15 in appendix B), thus as the contribution of the medical aid scheme to the total prescription cost increased, the percentage contribution of the patient decreased, and because prescriptions claimed for males had a higher average cost, the average amount per prescription paid by a male patient was higher. However, the

d-values between the average prescription cost between male and female biologics users indicated that the higher average cost per prescription for a male patient was not practically significant. The *d*-value remained below 0.8 and varied between 0.26, 0.42, 0.38 and 0.29 during the four years.

4.3.2.3 Total annual medicine expenditure and the contribution of the medical aid scheme and the patient to the total medication cost according to gender

From Table 4.4.6 it was calculated that prescriptions claimed by the female target population contributed 0.37% of the total medicine expenditure for 2005, whereas the male target population contributed 0.17% of the total medicine expenditure for that year. In 2006, the female target population's contribution to the total annual prescription cost increased to 0.63%, and the male target population's contribution increased to 0.33% of the total prescription cost for that year. The contributions of both the female and the male target population to the total annual medicine expenditure increased with another 0.59% for females and 0.46% for males between 2006 and 2008, and the contributions of the female and male populations to the total medicine expenditure in 2008 was 1.22% and 0.79% respectively.

When the total annual expenditure toward those prescriptions that contained biologic medicine items between 2005 and 2008 was calculated as percentages of the total annual medicine expenditure per gender group for the total database, the percentage values (as in Table 4.4.6) were determined.

Table 4.4.6 shows that biologic prescriptions claimed by female patients contributed 0.068%, 1.068%, 1,679% and 2.057% of the total amount spent on all the prescriptions claimed by female patients in 2005, 2006, 2007 and 2008 respectively. Biologic prescriptions for male patients on the other hand contributed 0.430%, 0.821% 1.530% and 1.924% of the total medicine expenditure for all the prescriptions claimed by male patients in 2005, 2006, 2007 and 2008 respectively. Female patients who received biologics thus contributed a larger portion to the final annual medicine expenditure than males during the four years (see Figure 4.14), which was expected since females represented a larger percentage of the total patient population who received biologics between 2005 and 2008.

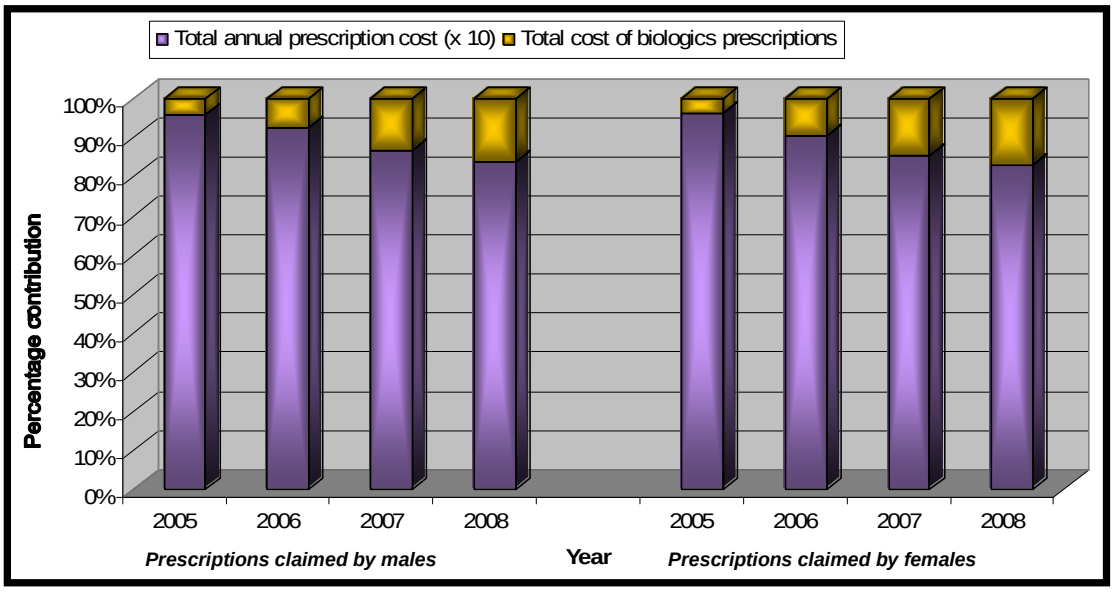

Figure 4.14 Percentage contribution of biologic prescriptions to the total annual prescriptions cost according to gender

The contribution to the total annual prescription cost of biologic prescriptions claimed by female patients increased with 1.989% between 2005 and 2008, whereas the contribution of biologic prescriptions claimed by male patients increased with 1.494% between 2005 and 2008 (refer to Table 4.4.6). Between 2005 and 2008 the percentage contribution of the medical aid scheme to the final prescription cost was roughly the same for both male and female patients who received biologics – approximately 96% to 97% of the final prescription cost was paid by the medical aid scheme each year, and the remaining 3% to 4% was co-paid by the patient (refer to Tables A.14 and A.15 in appendix B).

From the various values and percentages calculated from Table 4.4.6, it has been indicated that the costs of prescriptions of female patients who received biologics during the four study years, had a greater impact on the total annual medicine expenditure between 2005 and 2008, as their prescriptions contributed a reasonably larger percentage of the final prescription costs for each year, which might be attributed to the fact that there were more female patients.

4.3.2.4 Summary of analysis of target population according to gender

The analysis done from Table 4.4.6 indicates the following: out of all the patients who received biologics between 2005 and 2008, most of the patients were female each year. The difference between the number of male and female biologics users however decreased from 2005 to 2008 with 5.59%. When the number of females who received biologics each year

was calculated as a percentage of the total number of female patients on the database, and the same was done for male patients, the percentage female patients who received biologic medicine between 2005 and 2008 was still considerably higher than the percentage male patients who received biologics during the same time period (refer to Table 4.4.5). This may be ascribed to the fact that most of diseases for which these six biologic immunomodulators are indicated (i.e. rheumatoid arthritis, multiple sclerosis, Crohn's disease and cancer), mostly burden women (refer to section 2.7 in chapter 2).

Furthermore, the percentage females who received biologics increased with 0.033% from 2005 to 2008, whereas the percentage male patients who received biologics increased with 0.026% between 2005 and 2008. Thus, both the percentage of male and female patients who received biologics, increased each year, even though the total population of the database decreased each year between 2006 and 2008 (refer to Table 4.4.5). This might be because the prevalence of the disease for which these biologics are used increased in the patient population of the database, or because the mix of patients on the database changed (refer to section 4.2.1) and new patients with these diseases joined the medical aid schemes.

The analysis of the prescriptions of the target population portrayed basically the same results as for the number of patients: the larger percentage of all of the prescriptions that contained biologic medicine items between 2005 and 2008 was claimed for female patients. Out of all the prescriptions claimed for the total number of males and females in the total database, the percentage of female biologics prescriptions was more than the percentage male biologics prescriptions, as between 0.019% and 0.053% of all the prescriptions claimed for female patients, and only between 0.011% and 0.039% of all the prescriptions claimed for male patients were for biologic immunomodulators between 2005 and 2008 (refer to Table 4.4.6). This is most likely because there were more female patients than males who received biologic immunomodulators during the study period.

Table 4.4.6 furthermore showed that the percentages spent on those prescriptions that contained biologics increased each year between 2005 and 2008 for both female and male patients, but that the percentage spent on prescriptions that contained biologic medicine items was greater for female patients than for males, even though the average cost per biologics prescription was higher for a male patient than the average cost per biologics prescription for a female patient. The reason for the larger total medication cost of females is obviously because they received more biological medicine items than males. Thus, when the cost impact of biologic immunomodulators on the total annual medicine expenditure is considered, the female patients who received these medicine items between 2005 and 2008 had the biggest influence.

4.3.3 Analysis of target population according to age

Table 4.4.7 compares the number of patients of the total database with the number of patients of the target population according to age, as well as the average number of prescriptions per patient.

4.3.3.1 Number of patients and average number of prescriptions per patient per year according to age groups

Table 4.4.7.1 shows what percentage of patients who received biologic immunomodulators each year was represented by each age group. (Age group one = patients younger than 25 years; age group two = patients between 25 and 39 years; age group tree = patients between 40 and 64 years; age group four = patients older than 64 years).

Table 4.4.7.1 Number of patients and average number of prescriptions per patient per year according to age groups

TOTAL DATABASE					BIOLOGIC IMMUNOMODULATORS					
Year	Age group	Frequency (n = Patients)	Prescrip-tions	Average Rx per patient	Year	Age group	Frequency (n = Patients)	% n	Prescrip-tions	Average Rx per patient
2005	1	493,907	1,552,841	3.14 ± 3.32	*2005*	1	9	0.002	53	5.89 ± 4.51
	2	291,872	1,319,940	4.52 ± 5.09		2	34	0.012	242	7.11 ± 5.55
	3	556,022	3,669,930	6.60 ± 7.29		3	106	0.020	743	7.01 ± 4.86
	4	167,820	1,849,125	11.02 ± 10.19		4	49	0.029	281	5.73 ± 4.99
2006	1	499,442	1,633,373	3.27 ± 3.46	*2006*	1	12	0.002	79	6.58 ± 4.44
	2	300,056	1367,114	4.56 ± 5.25		2	53	0.018	463	8.74 ± 4.99
	3	588,107	3,968,127	6.75 ± 7.46		3	154	0.026	1,190	7.23 ± 4.47
	4	170,485	1,937,730	11.37 ± 10.54		4	60	0.035	322	5.37 ± 3.41
2007	1	394,672	1,397,144	3.54 ± 3.68	*2007*	1	16	0.004	117	7.31 ± 3.98
	2	202,901	1,112,243	5.48 ± 5.74		2	69	0.034	590	8.55 ± 4.88
	3	447,503	3,563,317	7.96 ± 7.94		3	202	0.045	1,723	8.53 ± 4.32
	4	133,520	1,838,380	13.77 ± 10.72		4	85	0.064	541	6.36 ± 4.31
2008	1	293,599	1,034,765	3.52 ± 3.78	*2008*	1	16	0.005	116	7.25 ± 4.93
	2	152,974	836,129	5.37 ± 5.89		2	58	0.038	507	8.74 ± 4.43
	3	400,575	3,172,125	7.92 ± 7.97		3	246	0.061	1,941	7.89 ± 4.86
	4	127,349	1,732,844	13.61 ± 10.93		4	96	0.075	629	6.55 ± 4.57

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

$\%n = n_{\text{biologic immunomodulators}} / n_{\text{total database}} \times 100$

From Table 4.4.7.1 it can be calculated what percentage of all the patients who received biologics each year belonged to which age group. Table 4.4.7.2 summarises these percentages for 2005 to 2008.

Table 4.4.7.2 Percentage distribution of the total number of patients who received biologic immunomodulators each year according to age groups

	2005	**2006**	**2007**	**2008**
Total number of patients who received biologic immunomodulators	**n = 198 100%**	**n= 279 100%**	**n = 372 100%**	**n = 416 100%**
Age group 1	4.55%	4.30%	4.30%	3.85%
Age group 2	17.17%	19.00%	18.55%	13.94%
Age group 3	53.54%	55.20%	54.30%	59.13%
Age group 4	24.75%	21.51%	25.81%	23.08%

Table 4.4.7.2 shows that the largest percentage of patients who received biologic immunomodulators between 2005 and 2008 were between the ages of 40 and 64 years (age group three), whereas patients younger than 25 years (age group one) represented the smallest percentage of all the patients who received biologic immunomodulators during the study period.

When the number of patients who received biologics each year is calculated as a percentage of the total number of patients in each age group, the percentage values (shown in Table 4.4.7.1 as %n) is determined, which indicates what percentage of each age group received biologics each year. Table 4.4.7.1 shows that out of all the patients who were younger than 25 years between 2005 and 2008, the percentage that was represented by patients who received biologics was 0.002% (n = 9) in 2005, 0.002% (n = 12) in 2006, 0.004% (n = 16) in 2007 and 0.005% (n = 16) in 2008. From 2005 to 2008, there was thus a 0.003% increase in the percentage patients in age group one who received biologics. Patients between 25 and 39 years (age group two) who received biologics in 2005 represented 0.012% (n = 34) of the entire patient population of the database between 25 and 39 years. In 2006, 0.018% (n = 53) of all patients in age group two received biologics, whereas 0.034% (n = 69) and 0.038% (n = 58) of all the patients in age group two received biologics in 2007 and 2008 respectively. The percentage patients aged between 25 and 39 years who received biologics thus increased with 0.026% during the four-year study period. Patients between 40 and 64 years (age group three) represented the largest percentage of the total database for the total duration of the study period (refer to Table 4.3.3). In 2005, 0.02% (n = 106) of all patients on

the database aged between 40 and 64 years received biologics. In 2006, 0.026% (n = 154) of all the patients in age group three received biologics, whereas 0.045% (n = 202) and 0.061% (n = 246) of all the patients between the ages of 40 and 64 years received biologics in 2007 and 2008 respectively. There was thus a 0.041% increase in the percentage of biologics users aged between 40 and 64 between 2005 and 2008 (refer to Tables 4.4.7.1 and 4.4.7.2). In 2005, 0.029% (n = 49) of all the patients older than 64 years (age group four) received biologics, whereas 0.035% (n = 60) and 0.064% (n = 85) of all the patients older than 64 years received biologics in 2006 and 2007 respectively. In 2008, 0.075% (n = 96) of all the patients in age group four received biologics. The percentage patients older than 64 years who received biologics thus increased with 0.04% from 2005 to 2008 (refer to Tables 4.4.7.1 and 4.4.7.2).

Figure 4.15 illustrates the percentage of patients in each age group who received biological medicine items between 2005 and 2008.

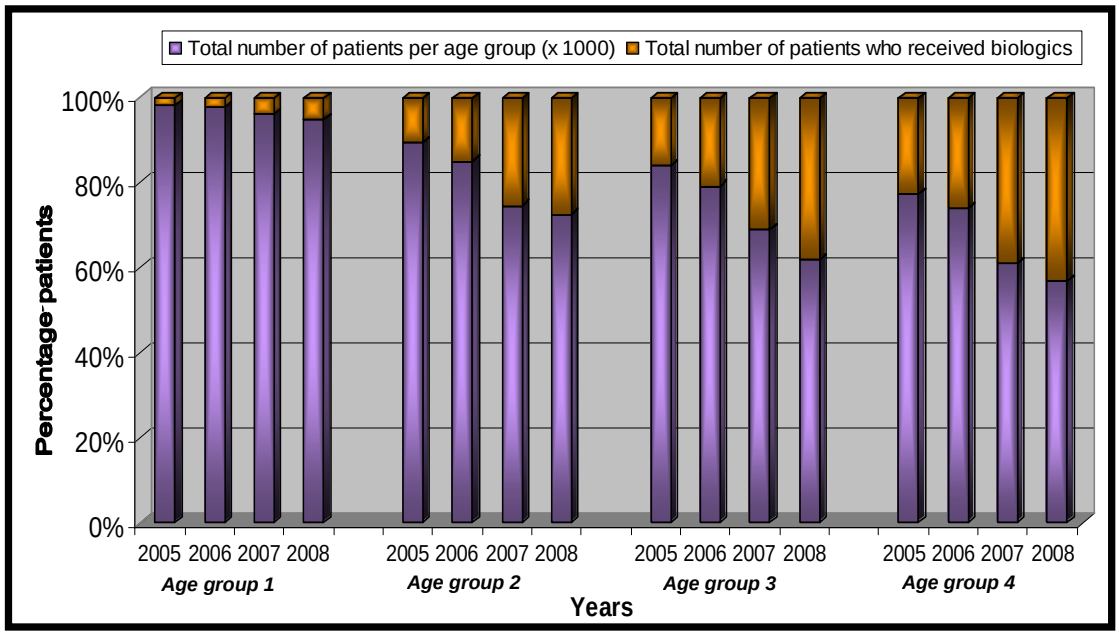

Figure 4.15 Percentage patients in each age group who received biologic immunomodulators each year

From Figure 4.15 it is evident that there were a relatively small number of the patients younger than 40 years (age groups one and two), and patients older than 64 years (age group four) who received biologics between 2005 and 2008 in comparison to the number of patients between 40 and 64 years (age group three) who received biologics during this time. According to Table 4.4.7, there were also a larger percentage of patients who received

biologic immunomodulators in age group three than in any other age group. The percentage patients per age group that was represented by patients who received biologic immunomodulators was thus also the largest for age group three, whereas age group one had the smallest percentage of patients who received biologic immunomodulators each year for all four years.

For the total database, patients younger than 25 years received an average of between 3.14 ± 3.32 (2005) and 3.52 ± 3.78 (2008) prescriptions per year, whereas for the target population, patients younger than 25 years received an average of between 5.89 ± 4.51 (2005) and 7.25 ± 4.93 (2008) prescriptions per patient per year. The average number of prescriptions for patients between 25 and 39 years per year for the total database was between 4.52 ± 5.09 (2005) and 5.37 ± 5.89 (2008) per patients for the study period and between 7.11 ± 5.55 (2005) and 8.74 ± 4.43 (2008) for patients who received biologics. Patients of the total database who were between 40 and 64 years received an average of between 6.60 ± 7.29 (2005) and 7.92 ± 7.97 (2008) prescriptions per year, whereas patients of the target population aged between 40 and 64 years received an average of between 7.01 ± 4.86 (2005) and 7.89 ± 4.86 (2008) prescriptions per year. Patients of the total database older than 64 years received between 11.02 ± 10.19 (2005) and 13.61 ± 10.93 (2008) prescriptions per patient per year on average, whereas patients older than 64 years who received biologics received between 5.73 ± 4.99 (2005) and 6.55 ± 4.57 (2008) prescriptions per year on average (refer to Table 4.4.7).

4.3.3.2 Number of prescriptions and average cost per prescription according to age groups

Table 4.4.8.1 summarises the average cost per prescription and the frequencies of prescriptions that contained biologics for both the target population and the total database from 2005 to 2008 according to age groups. Table 4.4.8.2 was compiled from Table 4.4.8.1 and shows what percentage of all the prescriptions that contained biologic immunomodulators between 2005 and 2008 was represented by each age group.

Table 4.4.8.2 shows that of all the prescriptions that contained biologic immunomodulators between 2005 and 2008, the largest percentage was claimed for patients between 40 and 64 years (age group three), followed by patients between 25 and 39 years (age group two) and patients older than 64 years (age group four). Prescriptions claimed for patients younger than 25 years (age group one) represented the smallest percentage of the total number of prescriptions that contained biologic immunomodulators between 2005 and 2008.

Table 4.4.8.1 Number of prescriptions and average cost per prescription according to age groups

AVERAGE COST PER PRESCRIPTION ACCORDING TO AGE FOR TOTAL DATABASE						AVERAGE COST PER PRESCRIPTION ACCORDING TO AGE FOR BIOLOGIC IMMUNOMODULATORS							
Year	Age group	Variable	Frequency (n = Prescriptions)	Mean ± SD (R)	Total cost (R)	Year	Age group	Variable	Frequency (n = Prescriptions)	% Rx	Mean ± SD (R)	Total cost (R)	% R
2005	1	Total cost	1,552,841	154.41 ± 190.13	239,766,846.41	2005	1	Total cost	53	0.003	6448.71 ± 1443.03	341,781.53	0.143
		Scheme amount		138.39 ± 179.38	214,897,939.98			Scheme amount			5865.40 ± 2107.78	310,865.94	
		Patient levy		16.02 ± 53.97	24,868,906.43			Patient levy			583.31 ± 1875.21	30,915.59	
	2	Total cost	1,319,940	171.84 ± 289.74	226,818,610.94		2	Total cost	242	0.018	7642.94 ± 4262.52	1,849,592.22	0.815
		Scheme amount		155.67 ± 278.26	205,479,491.44			Scheme amount			7265.03 ± 4204.15	1,758,138.28	
		Patient levy		16.17 ± 66.25	21,339,119.50			Patient levy			377.91 ± 1366.81	91,453.94	
	3	Total cost	3,669,930	221.24 ± 358.41	811,952,830.36		3	Total cost	743	0.020	7028.01 ± 3631.55	5,221,815.06	0.643
		Scheme amount		196.47 ± 341.04	721,025,658.60			Scheme amount			6749.36 ± 3804.95	5,014,776.95	
		Patient levy		24.78 ± 84.72	90,927,171.76			Patient levy			278.65 ± 1314.00	207,038.11	
	4	Total cost	1,849,125	292.75 ± 419.52	541,326,963.92		4	Total cost	281	0.015	8690.29 ± 6455.77	2,441,972.20	0.451
		Scheme amount		249.33 ± 394.46	461,044,559.41			Scheme amount			8583.88 ± 6525.72	2,412,070.17	
		Patient levy		43.42 ± 97.67	80,282,404.51			Patient levy			106.41 ± 694.24	29,902.03	
2006	1	Total cost	1,633,373	155.59 ± 213.41	254,141,563.62	2006	1	Total cost	79	0.005	7455.00 ± 1401.56	588,945.03	0.232
		Scheme amount		135.98 ± 201.78	222,111,395.73			Scheme amount			7286.39 ± 1781.11	575,624.89	
		Patient levy		19.61 ± 63.22	32,030,167.89			Patient levy			168.61 ± 996.97	13,320.14	
	2	Total cost	1,367,117	171.66 ± 315.33	234,674,113.15		2	Total cost	463	0.034	7777.39 ± 3342.34	3,600,929.33	1.534
		Scheme amount		152.55 ± 302.11	208,554,713.53			Scheme amount			7486.26 ± 3514.56	3,466,139.94	
		Patient levy		19.11 ± 74.62	26,119,399.62			Patient levy			291.12 ± 1345.61	134,789.39	
	3	Total cost	3,968,128	224.41 ± 416.63	890,470,151.20		3	Total cost	1,190	0.030	9127.56 ± 4550.21	10,861,791.51	1.220
		Scheme amount		196.82 ± 400.70	781,008,788.47			Scheme amount			8931.51 ± 4705.71	10,628,500.40	
		Patient levy		27.59 ± 89.14	109,461,362.73			Patient levy			196.04 ± 1050.36	233,291.11	
	4	Total cost	1,937,730	299.55 ± 492.37	580,452,906.12		4	Total cost	322	0.017	12110.28 ± 7203.67	3,899,510.82	0.672
		Scheme amount		251.34 ± 470.10	487,035,053.63			Scheme amount			12078.16 ± 7199.91	3,889,167.05	

Table 4.4.8.1 Number of prescriptions and average cost per prescription according to age groups *(continued)*

		Patient levy		48.21 ± 109.03	93,417,852.49			Patient levy			32.12 ± 357.11	10,343.77	
2007	1	Total cost	1,397,144	163.89 ± 292.33	228,982,535.62	2007	1	Total cost	117	0.008	8827.06 ± 4168.25	1,032,765.46	0.451
		Scheme amount		136.79 ± 259.00	191,117,985.47			Scheme amount			8827.06 ± 4168.25	1,032,765.44	
		Patient levy		27.10 ± 122.80	37,864,550.15			Patient levy			0.00 ± 0.00	0.02	
	2	Total cost	1,112,243	185.86 ± 470.34	206,723,414.80		2	Total cost	590	0.053	8192.22 ± 2592.25	4,833,412.17	2.338
		Scheme amount		158.62 ± 449.21	176,421,796.24			Scheme amount			7970.19 ± 2784.25	4,702,409.75	
		Patient levy		27.24 ± 115.07	30,301,618.56			Patient levy			222.04 ± 1159.22	131,002.42	
	3	Total cost	3,563,317	246.49 ± 649.89	878,327,951.34		3	Total cost	1,723	0.048	10404.03 ± 6634.42	17,926,142.99	2.041
		Scheme amount		210.74 ± 616.78	750,921,044.36			Scheme amount			10096.84 ± 6811.61	17,396,857.49	
		Patient levy		35.76 ± 167.99	127,406,906.98			Patient levy			307.19 ± 1774.45	529,285.50	
	4	Total cost	1,838,392	328.68 ± 720.57	604,250,274.90		4	Total cost	541	0.029	13393.93 ± 7391.54	7,246,117.38	1.199
		Scheme amount		270.10 ± 671.64	496,546,206.85			Scheme amount			13065.05 ± 7425.60	7,068,193.89	
		Patient levy		58.59 ± 227.46	107,704,068.05			Patient levy			328.88 ± 2240.25	177,923.49	
2008	1	Total cost	1,034,765	176.65 ± 365.21	182,794,294.08	2008	1	Total cost	116	0.011	8574.12 ± 2043.46	994,598.45	0.544
		Scheme amount		144.98 ± 345.12	150,022,179.26			Scheme amount			8573.69 ± 2043.57	994,548.45	
		Patient levy		31.67 ± 90.49	32,772,114.82			Patient levy			0.43 ± 2.04	50.00	
	2	Total cost	836,129	202.39 ± 631.89	169,227,300.16		2	Total cost	507	0.061	8866.35 ± 4515.75	4,495,237.57	2.656
		Scheme amount		169.93 ± 597.93	142,085,583.63			Scheme amount			8486.31 ± 4772.72	4,302,561.02	
		Patient levy		32.46 ± 159.88	27,141,716.53			Patient levy			380.03 ± 1709.81	192,676.55	
	3	Total cost	3,172,135	263.81 ± 839.12	836,842,632.27		3	Total cost	1,941	0.061	10755.92 ± 8149.51	20,877,237.75	2.495
		Scheme amount		221.77 ± 810.00	703,481,122.70			Scheme amount			10570.75 ± 8198.35	20,517,833.75	
		Patient levy		42.04 ± 182.14	133,361,509.57			Patient levy			185.16 ± 1244.32	359,404.00	
	4	Total cost	1,732,844	344.52 ± 927.44	597,006,787.34		4	Total cost	629	0.036	14943.10 ± 12614.05	9,399,212.65	1.574
		Scheme amount		278.71 ± 887.57	482,959,343.33			Scheme amount			14717.68 ± 12590.63	9,257,423.35	
		Patient levy		65.82 ± 223.52	114,047,444.01			Patient levy			225.42 ± 1774.19	141,789.30	

Age group 1 = < 25 years; Age group 2 = 25-39 years; Age group 3 = 40-64 years; Age group 4 = ≥ 65 years.

%Rx = $n_{biologic\ immunomodulators}$ / $n_{total\ database}$ x 100

%R = total $cost_{biologic\ immunomodulators}$ / total $cost_{total\ database}$ x 100

Table 4.4.8.2 Percentage distribution of prescriptions that contained biologic immunomodulators according to age groups

	2005	2006	2007	2008
Total number of prescriptions for biologic immunomodulators	**n = 1,319 100%**	**n = 2,054 100%**	**n = 2,971 100%**	**n = 3,193 100%**
Age group 1	4.02%	3.85%	3.94%	3.63%
Age group 2	18.35%	22.54%	19.86%	15.89%
Age group 3	56.33%	57.94%	57.99%	60.79%
Age group 4	21.30%	15.68%	18.21%	19.70%

Based on Table 4.4.8.2, most of the biologic prescriptions claimed through the PBM between 2005 and 2008 were claimed for patients between 40 and 64 years. Figure 4.16 graphically illustrates the percentage distribution of biologics prescriptions between the four age groups in 2005 and again in 2008.

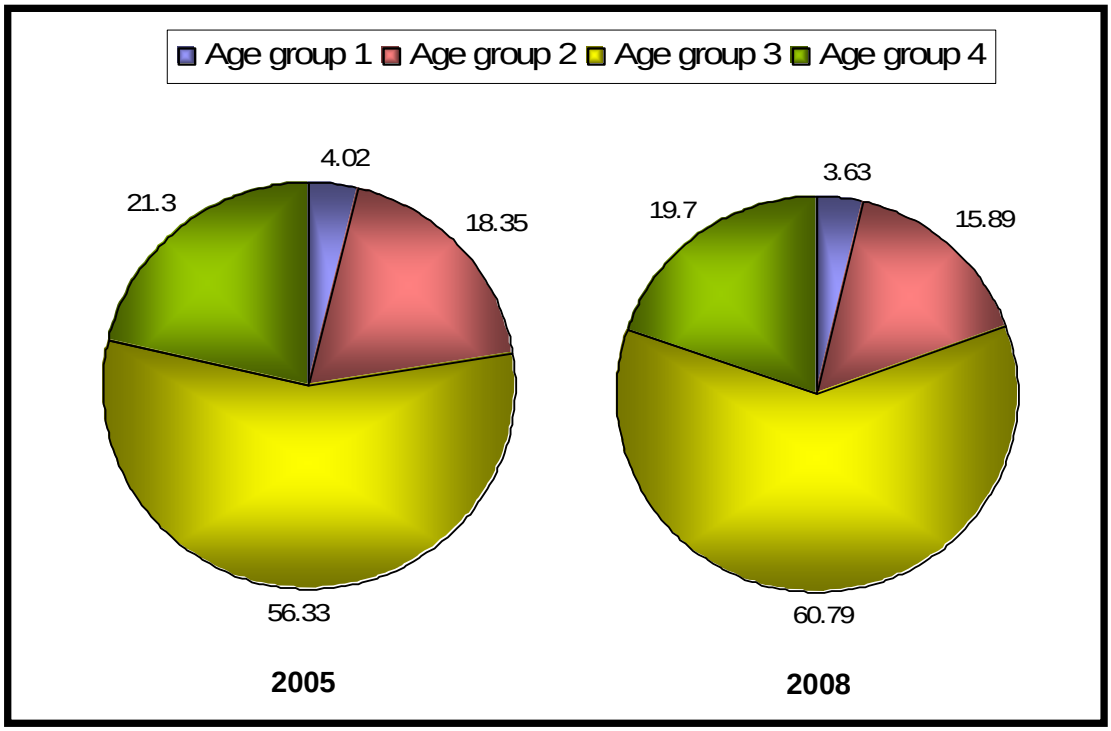

Figure 4.16 Percentage of total number of biologic prescriptions according to age groups: 2005 *vs* 2008

According to Table 4.4.8.2 and Figure 4.16, the percentage biologic prescriptions claimed for patients between 40 and 64 years (age group three) increased with 4.46% from 2005 to 2008, whereas the percentage biologic prescriptions represented by age groups one, two and four decreased between 2005 and 2008.

When the number of prescriptions that contained biologic immunomodulators between 2005 and 2008 were calculated as a percentage of the total number of prescriptions claimed per age group per year, the percentage values as shown in Table 4.4.8.1 (%Rx) were determined.

According to Table 4.4.8.1, 0.003% of the total number of prescriptions claimed for patients younger than 25 years in 2005 was represented by biologic prescriptions. This percentage increased with 0.002% between 2005 and 2006, and with another 0.003% between 2006 and 2007. In 2008, 0.011% of all the prescriptions claimed for patients younger than 25 years contained biologic immunomodulators, which means that the number of biologic prescriptions claimed for patients younger than 25 years increased with 0.008% between 2005 and 2008.

In 2005, 0.018% of the total numbers of prescriptions claimed for patients between 25 and 39 years was for biologic immunomodulators, and in 2006, 0.034% of the total number of prescriptions claimed for this age group was for biologic immunomodulators. In 2007, biologic prescriptions represented 0.053% of the total number of prescriptions claimed for patients between 25 and 39 years, whereas in 2008, 0.061% of the total number of prescriptions claimed for this age group was for biologic immunomodulators. The percentage biologic prescriptions claimed for patients between the ages of 25 and 39 years thus increased with 0.043% between 2005 and 2008 (refer to Table 4.4.8.1).

Based on Table 4.4.8.1, 0.020% of the total number of prescriptions claimed for patients between 40 and 64 years was for biologic immunomodulators. In 2006, 0.030% of all the prescriptions claimed for patients in this age group were for biologic immunomodulators, and the percentage increased further to 0.048% in 2007 and 0.061% in 2008. There was thus a 0.041% increase in the percentage prescriptions that contained biologic immunomodulators between 2005 and 2008 claimed for patients between 40 and 64 years.

Furthermore, according to Table 4.4.8.1, 0.015% of the total number of prescriptions that were claimed for patients in older than 64 years in 2005 was for biologic immunomodulators, and this percentage increased with 0.002% between 2005 and 2006. The increase in the percentage was larger between 2006 and 2007, as 0.029% of all the prescriptions claimed by patients older than 64 years in 2007 were for biologic immunomodulators. In 2008, 0.036% of all the prescriptions claimed by patients older than 64 years contained biologic immunomodulators, which means that the number of prescriptions claimed for patients older than 64 years that was represented by biologic immunomodulators, increased with 0.024% from 2005 to 2008.

Figure 4.17 shows that the percentage of the total number of prescriptions that was represented by biologics prescriptions increased for all four age groups each year.

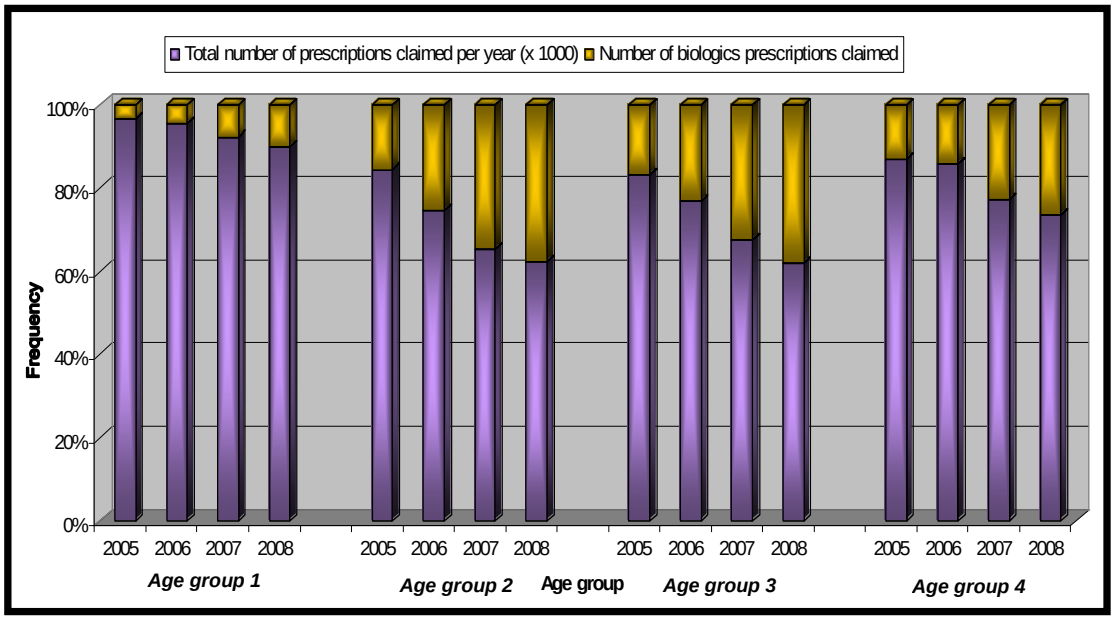

Figure 4.17 Percentage of the total number of prescriptions claimed per age group represented by biologic prescriptions

The percentage biologics prescriptions increased with 0.008% for age group one, 0.043% for age group two, 0.041% for age group three and 0.024% for age group four between 2005 and 2008. Table 4.4.8.1 and Figure 4.17 also show that out of all the age groups, age groups two and three had the highest percentage of prescriptions that contained biologic immunomodulators between 2005 and 2008, which means that it was mostly patients between the ages of 25 and 64 that received prescriptions for biologic immunomodulators during these four years. This makes sense, because of all the patients who received biologics between 2005 and 2008, most were older than 39 years (age groups three and four), and the least were younger than 25 years (age group one) (refer to Tables 4.4.7.1 and 4.4.7.2).

Table 4.4.8.1 furthermore indicates that the average cost per biologic prescription increased for all four age groups each year. The average cost per biologic prescription for patients younger than 25 years (age group one) increased with 32.96% between 2005 and 2008, whereas the average cost per biologic prescription for patients between 25 and 39 years (age group two) increased with 10.01% during the same period. The average cost per prescription that contained a biologic immunomodulator for a patient between 40 and 64 years (age group three) increased with 53.04% between 2005 and 2008, and the average

cost per biologic prescription for patients older than 64 years increased with 71.95% from 2005 to 2008.

When the average cost per prescription between the four age groups is compared, it is evident that the average cost per prescription that contained a biologic immunomodulator differed from one age group to another. Figure 4.18 (compiled from Table 4.4.8.1) illustrates the difference in the average cost per biologic prescription between the four age groups.

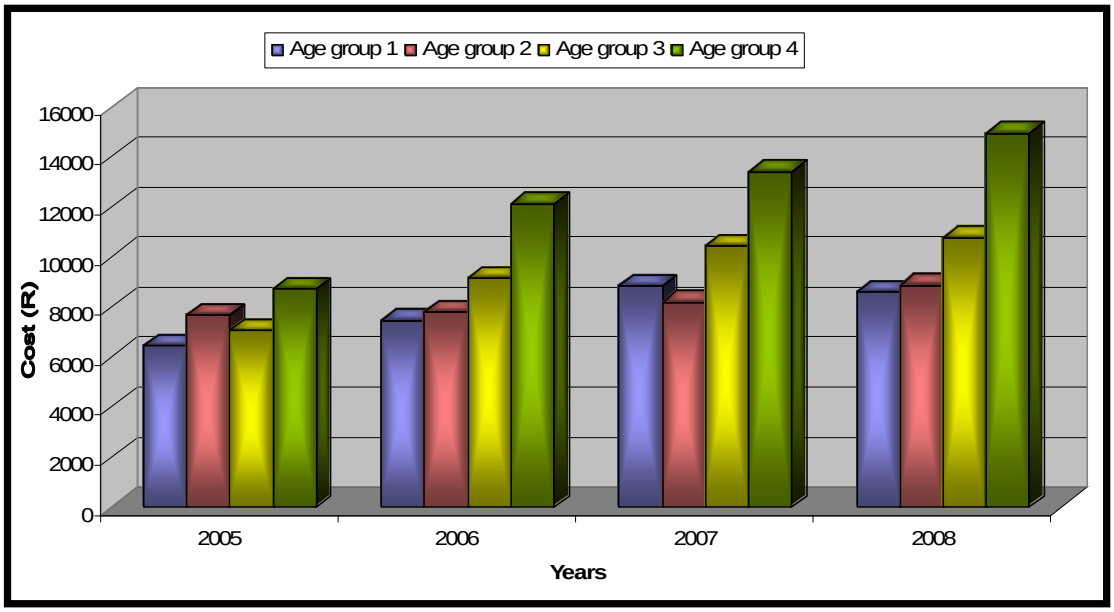

Figure 4.18 Average cost per biologic prescription per patient per year according to age groups

Figure 4.18 indicates that the average cost of a biologic prescription was higher for patients who were older than 64 years (age group four) between 2005 and 2008 than for patients younger than 65 years. In 2005, the average cost per biologic prescription for a patient older than 64 years was about 35% more than the average cost per biologic prescription for a patient younger than 25 years (age group one), 13.70% higher than the average cost per biologics prescription for a patient in age group two and 23.65% higher than the average cost per biologics prescription for a patient in age group three (refer to Table 4.4.8.1).

In 2008, a biologic prescription for a patient in age group four was 74.28% higher than the average cost per biologic prescription for a patient in age group one, and 68.54% and 38.93% higher than the average cost per biologic prescription for patients in age groups two and three respectively (refer to Table 4.4.8.1). The *d*-values indicate that the difference between the average biologic prescription cost between age group four and age groups one and two had a medium effect (*d*-value = 0.5) that might be practically significant, but that the

difference between the average cost per biologic prescription between age groups four and three was not practically significant (*d*-value = 0.3). Furthermore, the average amount paid by the both the medical aid scheme and the patient for a biologic prescription significantly increased between 2005 and 2008, even though the percentage of the total prescription cost paid by the medical aid scheme only increased slightly (approximately 1% to 3%) (refer to Tables A.17 to A.20 in appendix B). The average scheme amount for a biologic prescription for patients younger than 25 years increased with 46.17% from 2005 to 2008. For patients between 25 and 39 years, the average scheme amount increased with 16.81% and for patients between 40 and 64 years, the average scheme amount increased with 50.41% between 2005 and 2008. The average scheme amount increased the most for biologic prescriptions claimed for patients older than 64 years, as it increased with 65.10% between 2005 and 2008 (refer to Table 4.4.8.1).

The average patient levy also changed over the four years. The percentage contribution of the patient to the total prescription cost was relatively small (between 0% and 5%) during the four years (refer to Tables A.17 to A.20 in appendix B). For age groups one and three, this amount decreased between 2005 and 2008 – with 135,553% for patients younger than 25 years (age group one) and with 50.41% for patients between 40 and 64 years (age group three). The average patient levy per biologic prescription however increased for age groups two and four between 2005 and 2008. The increase in the average patient levy for biologic prescriptions claimed for patients between 25 and 39 years (age group two) was very low – only 0.56% - but the increase in the average patient levy for patients older than 64 years (age group four) was considerable, as the average patient levy for a biologic prescription claimed for a patient older than 64 years increased with 111.84% between 2005 and 2008 (refer to Table 4.4.8.1).

Thus, not only was the average cost per biologic prescription the highest for those patients older than 64 years, but the percentage increase in the average prescription cost was also the highest for these patients, as the average cost per biologic prescription for these patients was 71.95% higher in 2008 than in 2005 (refer to Table 4.4.8.1).

4.3.3.3 Total annual medicine expenditure and the contribution of the medical aid scheme and the patient to the total medication cost according to age groups

From Table 4.4.8.1 it was calculated that biologics claimed for patients younger than 25 years (age group one) contributed to 0.019% of the total medicine expenditure for 2005, whereas biologics claimed for patients between 25 and 39 years (age group two) contributed to 0.102% of the total medicine expenditure for that year. Biologics claimed for patients between 40 and 64 years (age group three) contributed to 0.287% of the total medication cost for 2005 and biologics claimed for age group four contributed to 0.134% of the total medicine expenditure for that year.

From 2005 to 2008, the contributions of all four age groups' biologic prescriptions to the total annual medicine expenditure increased. The contribution of biologics claimed for age group one and age group two to the total medicine expenditure for 2005 amounted to 0.056 % and 0.252% respectively. Biologics claimed for age group three in 2008 contributed to 1.169% of the total medicine expenditure for that year, whereas the biologics claimed for age group four contributed to 0.526% of the total cost of all the medication claimed through the PBM in 2008. The contribution of biologics claimed for age group one to the total medication cost thus increased with 0.037% between 2005 and 2008, whereas the contribution of biologics claimed for age group two to the total medication cost increased with 0.15% from 2005 to 2008. The contribution of biologics to the total annual medicine expenditure for age group three increased with 0.882% from 2005 to 2008, whereas the percentage contribution of biologics claimed for age group four to the total medication cost for 2008 was 0.392% larger than in 2005 (refer to Table 4.4.8.1).

It is evident that the contribution of biologic immunomodulators to the total annual medicine expenditure increased for all four age groups between 2005 and 2008. It is also evident that the contribution of biologic immunomodulators claimed for patients between 40 and 64 years to the total annual medicine expenditure was larger than the contribution made by biologics claimed for any of the other age groups' biologics (refer to Table 4.4.8.1).

When the total annual expenditure toward biologics between 2005 and 2008 was calculated as percentages of the total annual medicine expenditure per age group for the total database, the percentage values (shown as %R in Table 4.4.8.1) were determined.

Table 4.4.8.1 shows that biologics claimed for patients younger than 25 years (age group one) contributed 0.143%, 0.232%, 0.451% and 0.544% of the total amount spent on all the prescriptions claimed for patients younger than 25 years in 2005, 2006, 2007 and 2008 respectively. The percentage contributed by biologics claimed for patients in age group one

to the total medication cost of this age group thus increased with 0.401% between 2005 and 2008 (refer to Table 4.4.8.1).

Biologics claimed for patients between 25 and 39 years (age group two) contributed 0.815%, 1.534%, 2.338% and 2.656% of the total medicine expenditure for this age group in 2005, 2006, 2007 and 2008 respectively, which shows that the percentage contribution of biologics to the total medication cost for this age group increased with 1.841% between 2005 and 2008 (refer to Table 4.4.8.1).

Biologics claimed for patients between 40 and 64 years (age group three), on the other hand, contributed 0.643%, 1.220%, 2.041% and 2.495% of the total medicine expenditure for patients in this age group in 2005, 2006, 2007 and 2008 respectively. The percentage of the total medication cost for patients between the ages of 40 and 64 years contributed by biologics thus increased with 1.854% between 2005 and 2008 (refer to Table 4.4.8.1).

Biologics claimed for patients older than 64 years (age group four) contributed 0.451%, 0.672%, 1.199% and 1.574% of the total medicine expenditure for all the patients older than 64 years between 2005 and 2008. The percentage of the total medication cost for age group 4 contributed by biologics prescriptions thus increased with 1.123% between 2005 and 2008 (refer to Table 4.4.8.1). Figure 4.19 shows what percentage of each age group's annual prescription cost was contributed by biologics prescriptions.

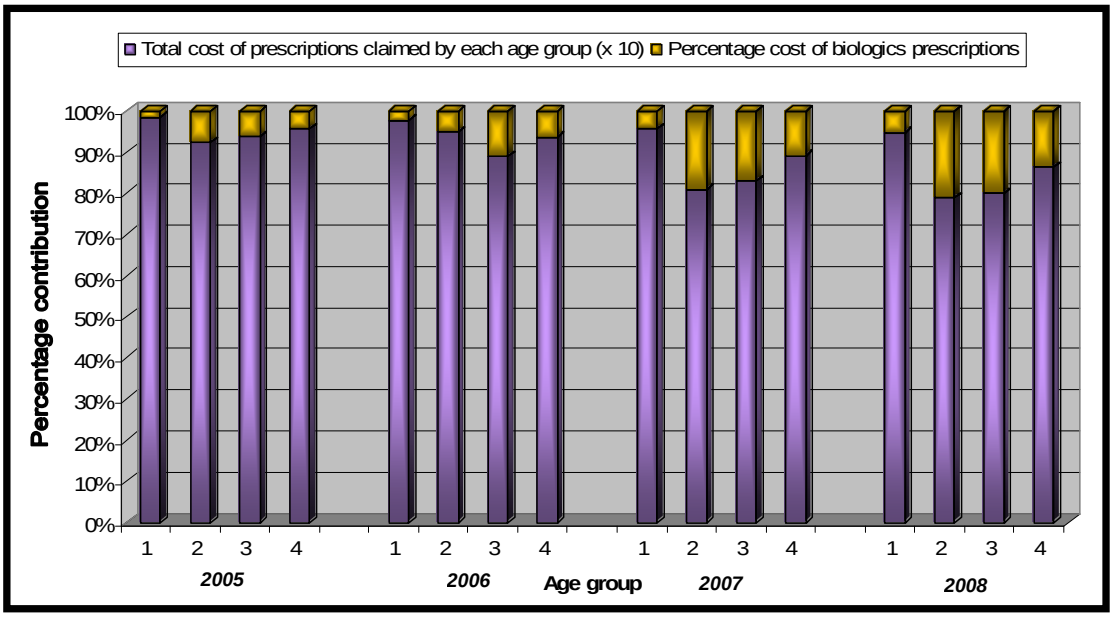

Figure 4.19 Contribution of biologic prescriptions to the total annual prescription cost

According to Figure 4.19, patients in age groups two (25 to 39 years) and three (40 to 64 years) who received biologics between 2005 and 2008 contributed a larger portion to the final annual medicine expenditure for their age group than any of the other three age groups during the four years.

Furthermore, based on Figure 4.19, the contribution of biologics to the total annual medication cost of all four age groups increased between 2005 and 2008. The contribution of biologics claimed for age group one to the total cost of all the medication claimed for that age group, increased with 0.041%% between 2005 and 2008, whereas the contribution of biologics claimed for age group two increased with 1.841% between 2005 and 2008. Biologics' contribution to the total annual medication cost of all the medication claimed for age group three increased with 1.854%% between 2005 and 2008, whereas the contribution of biologics claimed for age group four increased with 1.123% between 2005 and 2008 (refer to Table 4.4.8.1).

Thus, when the cost impact of biologics on the total annual medication cost is considered, biologics claimed for patients between 25 and 64 (age groups two and three) had the largest impact on the annual medicine expenditure between 2005 and 2008 (refer to Table 4.4.8.1). Figure 4.20 shows how the cost of biologics claimed for each age group compared to the total prescription cost per age group per year.

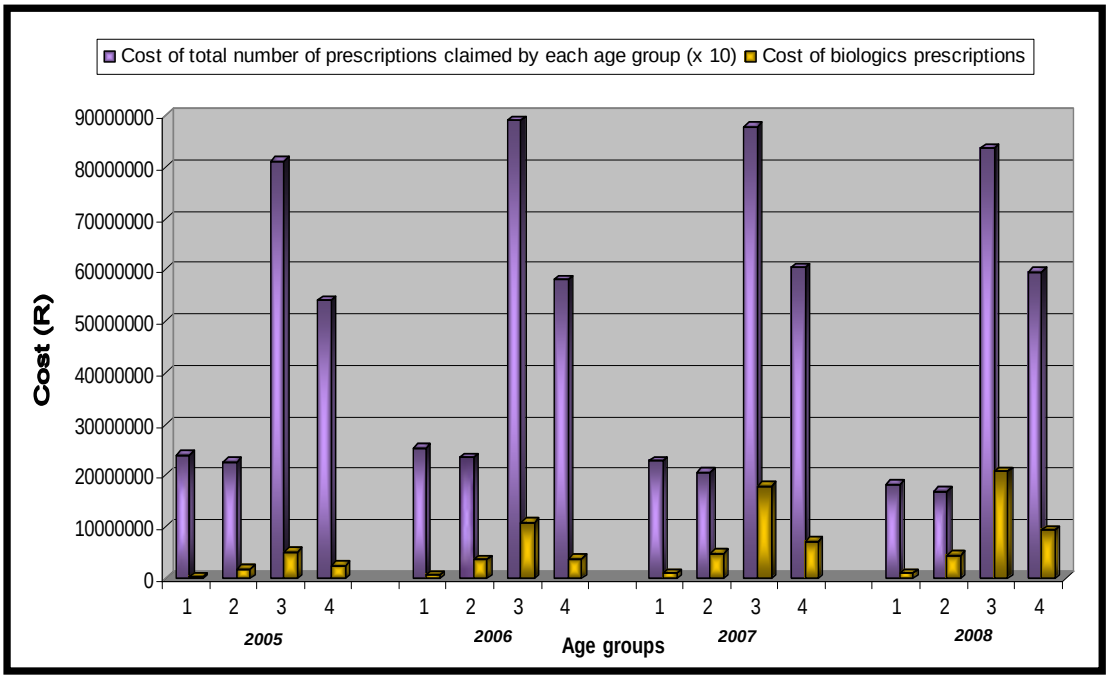

Figure 4.20 Total cost of biologics per age group compared to the total medication cost per age group per year

From Table 4.4.8.1 is can be calculated that the percentage contribution of the medical aid scheme and the contribution of the patient to the final prescription cost was roughly the same for biologics prescriptions for all age groups – approximately 95% to 100% of the final prescription cost was paid by the medical aid scheme each year, and the remaining percentage was co-paid by the patient (refer to Tables A.17 to A.20 in appendix B). However, there was a rather considerable difference in the contribution of the medical aid scheme to the total prescription cost between biologic immunomodulators and medication on the total database during the four years. Figure 4.21 illustrates the percentage contributions of the medical scheme and the patient to the total cost of all the medication on the total database and the total cost of biologic immunomodulators for 2005 and 2008.

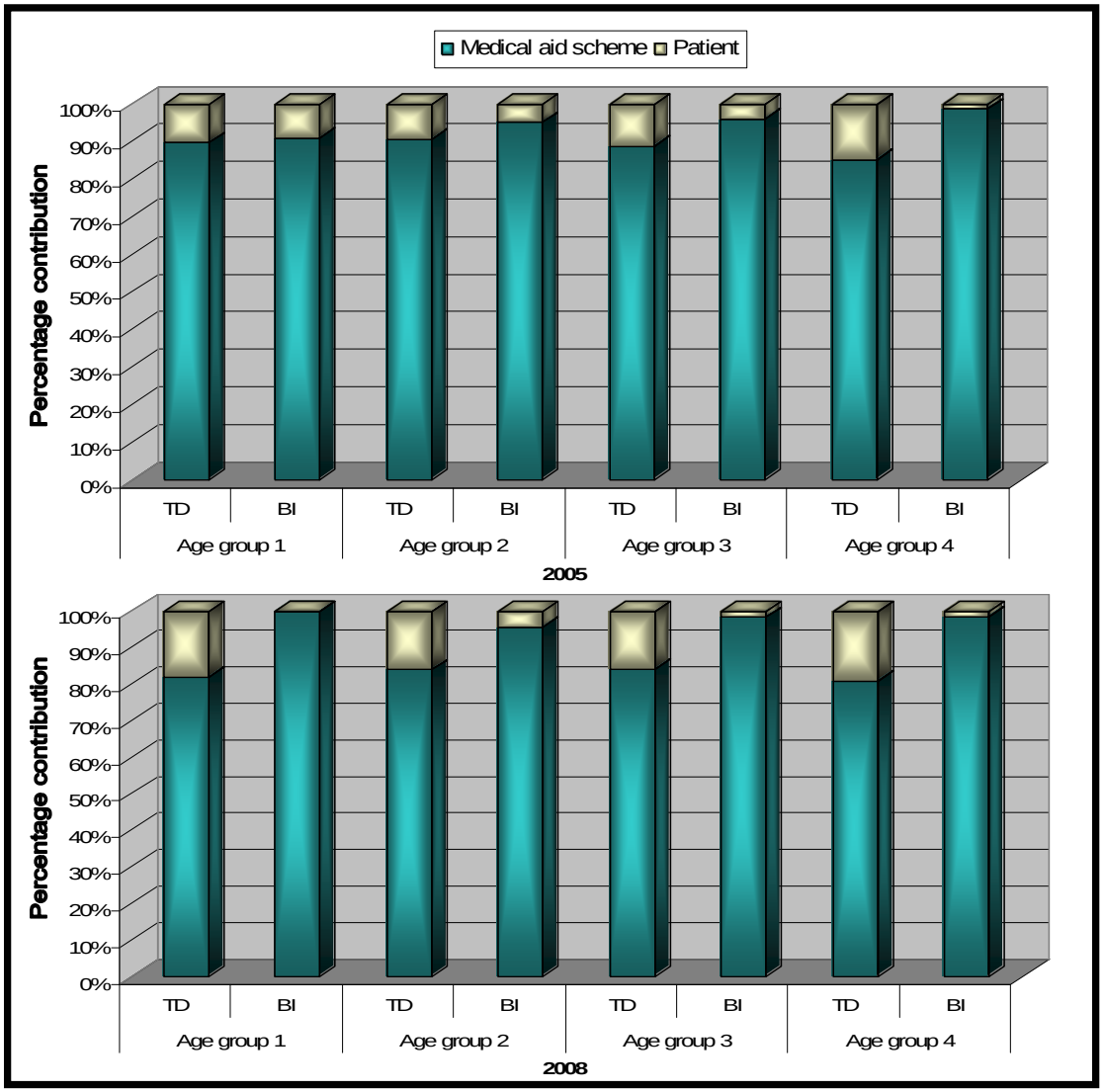

Figure 4.21 Percentage of the total prescription cost contributed by the medical aid scheme and patient for the total database prescriptions *and* biologic prescriptions between 2005 and 2008

Based on Figure 4.21, the percentage contribution of the medical aid scheme was the largest for biologics claimed for patients older than 64 years (age group four), whereas the percentage of the total cost of biologics contributed by the patient was the largest for patients younger than 25 years (age group one) between 2005 and 2008 (refer to Tables A.17 to A.20 in appendix B).

4.3.3.4 Summary of the analysis of the target population according to age groups

The analysis done from Table 4.4.8.1 indicated that out of the total number of patients who received biologics between 2005 and 2008, most of the patients were between the ages of 40 and 64 years. It was also concluded that the percentage patients who received biologics each year increased for all four age groups between 2005 and 2008, even though the total number of patients of the total database decreased. This might be because more patients on the database required these medicine items each year, or because the mix of the patient population of the database changed and patients who had already received biological medicine items joined the medical aid scheme during the four-year period (refer to section 4.2.1).

When the number of patients who received biologics each year was calculated as a percentage of the total number of patients in each age group, the percentage patients in age group three who received biologic medicine between 2005 and 2008 was higher than the percentage patients who received biologics in any other age group during the same time period, and age group one had the smallest percentage of patients who received biologic immunomodulators each year for all four years (refer to Table 4.4.8.1).

Table 4.4.8.1 furthermore showed that of the total number of prescriptions that contained biologic immunomodulators between 2005 and 2008, the largest percentage was claimed by age group three, but out of all the prescriptions claimed by the total number of patients in each age group, the percentage of biologics prescriptions claimed by age group two was more than the percentage biologics prescriptions claimed by any other age group. Thus, out of all the age groups, age groups two and three had the highest percentage of prescriptions that contained biologic immunomodulators between 2005 and 2008, which means that it was mostly patients between the ages of 25 and 64 that claimed prescription for biologic immunomodulators during these four years. This was expected since most of the patients who received biologics between 2005 and 2008 were between the ages of 40 and 64 years (age group three), and the smallest portion of patients were younger than 25 years (age group one) (refer to Table 4.4.7.1).

Table 4.4.8.1 furthermore shows that the percentages spent on those prescriptions that contained biologics increased each year between 2005 and 2008 for all four age groups, but that the percentage spent on prescriptions that contained biologic medicine items was greater for patients older than 64 than for patient younger than 64. The average cost per biologics prescription was also higher for a patient older than 64 than the average cost per biologics prescription for patient younger than 64. Thus, when the cost impact of biologic immunomodulators on the total annual medicine expenditure is considered, it was patients between the ages of 25 and 64 years, who received these medicine items between 2005 and 2008, who had the biggest influence.

4.3.4 Summary of the target population

The number of patients who received biologic immunomodulators increased each year, even though the total number of patients in the total database decreased between 2006 and 2008. The number of patients who received these medicine items increased with 110% between 2005 and 2008, as the number of biologics users was more than twice as many in 2008 than in 2005.

Most of the patients who received biologics between 2005 and 2008 were female (more than two thirds of all the biologics users), and most patients who received these medicine items were between the ages of 39 and 64, followed by those patients aged between 25 and 39.

The percentage contribution of biologic immunomodulators to the total number of items and prescriptions, as well as to the total medicine expenditure of the total database, was relatively small, but the rate at which the contributions increased was significant. The percentage contribution of biologic immunomodulators to the total number of medicine items and prescriptions on the total database increased each year, and in four years' time, the percentage of all the medicine items and prescriptions on the total database that were represented by biologic immunomodulators had tripled.

The percentage contribution of biologic immunomodulators to the total medicine expenditure also increased from one year to another for the four-year study period, and between 2005 and 2008 the percentage contribution of biologic immunomodulators to the total annual medicine expenditure had quadrupled. The increase in the cost of these agents was thus greater than the increase in their frequency.

This is explained by the average cost of a biologic immunomodulator and the average cost per prescription that contained biologic immunomodulators. The average cost per biologic immunomodulator was 60 times more than the average cost of a non-biologic medicine item. Furthermore, the average cost per biologic medicine item increased with 71.10% between 2005 and 2008, whereas the average cost per non-biologic medicine item increased with 16.41% between 2005 and 2008.

The average cost per biologics prescription increased every year. The increase in the average cost of a biologics prescription was also somewhat more than the increase in the cost of a non-biologic prescription – the average cost per non-biologic prescription increased with 21.5% between 2005 and 2008, whereas the average cost per biologics prescription increased with 49.92% during the four years.

The percentage of the final prescription cost that was contributed by the medical aid scheme increased for biologic immunomodulators, whereas it decreased for non-biologics prescriptions. Even though the percentage contribution of the medical aid scheme to the total cost of a biologics prescription did not increase much between 2005 and 2008 (approximately with 2%), the average amount that had to be paid by the medical aid scheme for a biologics prescription increased with 52.57% between 2005 and 2008. The average amount that was co-paid by a patient who received a biologics prescription decreased with 25.34%.

On the other hand, for a non-biologic prescription, the average amount co-paid by the patient increased between 2005 and 2008. The average amount co-paid by the patient was 75.07% more in 2005 than in 2008, whereas the average amount contributed by the medical aid scheme was 14.28% more in 2008 than in 2005, even though the percentage contribution of the medical aid scheme to a non-biologics prescription decreased with 6% during that time.

It can thus be concluded that even though biologic immunomodulators were used by only a very small percentage of the total database population, they were relatively expensive and had a considerable impact not only the medical aid scheme, but also on the patient.

4.4 General analysis of selected autoimmune diseases

In this section, a general analysis of the three autoimmune diseases discussed in this dissertation was conducted. Figure 4.22 illustrates how the results of section 4.4 were presented.

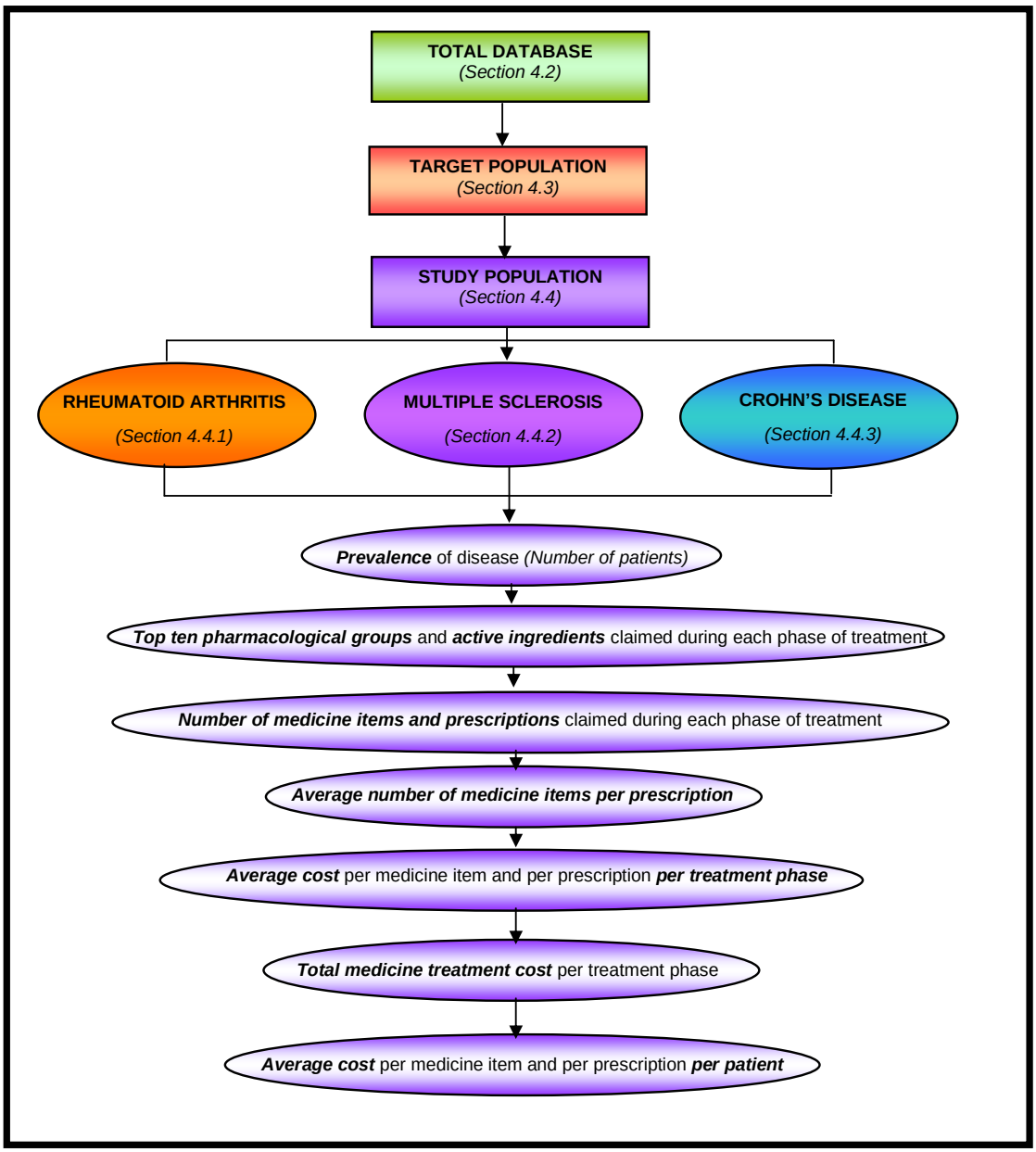

Figure 4.22 Presentation of results of section 4.4

The analysis of each autoimmune disease began with an analysis of the prevalence of the disease on the database, followed by an analysis of the top ten medicine items and pharmacological groups prescribed to patients during each phase of their treatment. Where there were more than one medicine item with the same frequency in the tenth position, all of the medicine items with that frequency were included. Furthermore, since not all medicine items are prescribed alone, the combinations in which the medicine items were prescribed were also discussed, but only to a maximum of four items per prescription, because even though there were cases in which more than four items were combined, the frequencies in which this happened seldom exceeded one. Additionally, in cases where there were countless combinations with a frequency of one, they were also excluded so that only those medicine items and combinations that were prescribed more than once during the four-year period were included.

Each analysis continued with the analysis of the frequencies and costs of all medicine items and prescriptions prescribed (both biologic immunomodulators and other medication) to patients during each phase of their treatment. Analysis of frequencies and costs of medicine treatment were also done according to gender, age and prescriber type.

4.4.1 Analysis of patients with Rheumatoid Arthritis (RA)

The patients discussed in this section includes all the patients who (i) received at least one of the six biologic immunomodulators discussed in this study at least once during the four-year study period, and (ii) had at least two positive diagnostic codes for RA (i.e. ICD-10 MPA code: M05/M06/M08, diagnosed code: RHA, ICD-10 claim code: RHA) at any time between 2005 and 2008.

4.4.1.1 Number of RA patients on the database between 2005 and 2008

Before the frequencies and costs of RA therapies can be investigated, it is first necessary to establish how many patients with RA received biologic immunomodulators during the study period. Table 4.5.1 (compiled from Tables A.26.1 to A.26.3 in appendix B) summarises the number of RA patients who received biologic immunomodulators between 2005 and 2008 and according to gender and age.

Table 4.5.1 Number of RA patients on the database between 2005 and 2008

Total number of patients	Number of patients according to gender		Number of patients according to age group			
141	***Male***	***Female***	***AG 1***	***AG 2***	***AG 3***	***AG 4***
	41	100	4	20	92	25

According to Table 4.5.4, a total of 141 patients with RA on the PBM database who claimed biologic immunomodulators between 2005 and 2008 could be seen. More than two thirds (70.92%) of these patients were female, giving a ratio of males to females as 1:2.44. The largest percentage (65.25%) of RA patients were between the ages of 40 and 64 years of age (age group three), patients older than 64 years (age group four) represented the second largest percentage of RA sufferers (17.73%), followed by patients in age group two (25 to 39 years) who represented 14.18% of RA patients between 2005 and 2008. There were only four patients diagnosed with RA who were younger than 25 years (2.84%). According to the literature, women are affected two to three times more often than men, and onset of RA is most often between 35 and 50 years (Beers, 2006:283). The division of the patient population with RA is thus in line with the literature.

4.4.1.2 Top ten medicine items and pharmacological groups claimed for RA patients during each phase

In this section, the top ten pharmacological groups and active ingredients were compiled for each of the three phases of RA treatment between 2005 and 2008. The top ten pharmacological groups claimed during each phase will also be compiled. Phases one and three only included non-biological medication (hence forth referred to as "*other medication*"), whereas phase two included both biologic immunomodulators and other medicines.

Tables 4.5.2.1 and 4.5.2.2 summarise the top ten pharmacological groups and top ten medicine items claimed for RA patients during phase one of their treatment. This includes all the medicine items claimed for RA patients before starting treatment with biological medicine items. According to Table 4.5.2.1, cytostatic agents were claimed most frequently during phase one of RA treatment, followed by the corticosteroids. The haematinic agents represented the third largest percentage of all medicines claimed for RA patients during phase one. However, haematinics (i.e. folic acid) is prescribed in combination with methotrexate (cytostatic agent) in order to help prevent serious side-effects (refer to Table

2.13 in chapter 2). Haematinics or folic acid will therefore not be viewed as an individual group, but as part of cytostatic agents or methotrexate. Therefore, after corticosteroids, analgesics and COX-inhibitors were the third (4.74%) and fourth (4.53%) most prevalent pharmacological groups claimed for RA patients during phase one (refer to Table 4.5.2.1).

Table 4.5.2.1 Top ten pharmacological groups claimed for RA patients during phase 1

Position	Pharmacological code	Description	Frequency	%n
1	23.1.1	Cytostatics	1,558	8.88
2	19.5.1	Corticosteroids	1,163	6.63
	8.6.1	Haematinics	1,098	6.26
3	3.3.1	Analgesics	831	4.74
4	4.1.1	COX-inhibitors	795	4.53
5	12.10.1	Gastro-intestinal tract	735	4.19
6	4.1.2	Selective COX-2 inhibitors	681	3.88
7	18.11.1	Antiprotozoal agents	502	2.86
8	12.4.4	Proton pump inhibitors	496	2.83
9	4.1.3	Specific cyclo-oxygenase-2 inhibitor	459	2.62
10	19.3.1	Thyroid agents	451	2.57
% n = frequency / 17550 **17550 = frequency of all the active ingredients claimed during phase 1**				

Table 4.5.2.2 Top ten active ingredients claimed for RA patients during phase 1

Position	Pharmacological code	Active ingredient name	Description	Frequency	%n
1	23.1.1	Methotrexate	Cytostatics	1,558	8.88
	8.6.1	Folic acid	Haematinics	1,037	5.90
2	19.5.1	Prednisolone	Corticosteroids	1,019	5.81
3	12.10.1	Sulphasalazine	Gastro-intestinal tract	706	4.02
4	4.1.2	Meloxicam	Selective COX-2 inhibitors	681	3.88
5	18.11.1	Chloroquine	Antiprotozoal agents	475	2.71
6	19.3.1	Thyroxine	Thyroid agents	451	2.57
7	4.1.1	Diclofenac	COX-inhibitors	408	2.32
8	4.6.1	Leflunomide	Musculo-skeletal agents (other)	373	2.13
9	4.1.3	Celecoxib	Specific cyclo-oxygenase-2 inhibitor	355	2.02
10	1.4.1	Amytriptyline	Trycyclic antidepressants	337	1.92
% n = frequency / 17550 **17550 = frequency of all the active ingredients claimed during phase 1**					

Based on Table 4.5.2.2, of the top ten active ingredients claimed for RA patients in phase one, methotrexate was claimed most frequently (together with folic acid), followed by prednisone, sulphasalazine and meloxicam. It is thus clear from Table 4.5.2.2, that the active ingredients claimed for RA patients before they started treatment with biologic immunomodulators, were the DMARDs (methotrexate, sulphasalazine, chloroquine, leflunomide), the corticosteroid prednisone, and various NSAIDs (meloxicam, diclofenac, celecoxib), which is in exact accord with the treatment algorithm of RA (refer to Figure 2.13 in section 2.7.1.7).

The combinations in which other medication were claimed for RA patients during the first phase of their treatment, are summarised in Table A.22.1 in appendix B. From Table A.22.1 it is clear that most combinations (indicated for RA) normally included a DMARD (methotrexate, sulphasalazine, Leflunomide, chloroquine) together with; another DMARD, and/or a NSAIM (ibuprofen, diclofenac, indometacin), and/or a selective COX-2 inhibitor (celecoxib) and/or a corticosteroid (prednisolone, bethametasone). Folic acid was also frequently prescribed with methotrexate. These combinations are also a true representation of the treatment protocol of RA (refer to Figure 2.13). DMARDs are indicated to slow the disease progression, whereas corticosteroids are indicated to treat the symptoms of RA, which is why it is often necessary to combine these agents in RA treatment (refer to section 2.7.1.7).

Table 4.5.3.1 summarises the biologic immunomodulators claimed for RA patients during phase two of their treatment.

Table 4.5.3.1 Biologic immunomodulators claimed for RA patients during phase 2

Position	Pharmacological code	Active ingredient	Description	Frequency	%n
1	4.6.1	Etanercept	Musculo-skeletal agent (other)	1,750	14.06
2	24.1.1	Adalimumab	Biologic	718	5.77
3	12.10.1	Infliximab	Gastro-intestinal tract (other)	96	0.77
4	23.1.1	Rituximab	Cytostatic	1	0.008
% n = frequency / 12446					

Based on Table 4.5.3.1, of all the active ingredients claimed during phase two, 20.61% were biologic immunomodulators. Etanercept represented 68.23% of all the biologic immunomodulators, whereas adalimumab represented 27.99% and infliximab represented 3.74%. Thus, the biologic immunomodulators claimed for RA patients were mostly the TNF-

α inhibitors (99.96%). This is in line with the treatment regime of RA, as according to the literature, TNF-α inhibitors are the biologics of choice for treating RA (refer to section 2.7.1.7). Even though it may be used to treat RA, the indication of rituximab for RA is very recent (Tak, 2010), which may explain why it was only claimed once for an RA patient during the four year period.

Furthermore, biologic immunomodulators were most often claimed alone. However, there were cases in which more than one biologic immunomodulator were claimed at the same time. Table A.22.2.2 in appendix B shows the combinations of biologic immunomodulators up to four items. The frequency at which adalimumab was claimed alone 694, the frequency at which etanercept was claimed alone indicated 1,643 and the frequency at which infliximab totalled was claimed alone showed as 81. Etanercept was the biologic immunomodulator where more than one medicine item was claimed simultaneously (i.e. more than one medicine item with etanercept as active ingredient on one prescription) most frequently (n = 50), followed by adalimumab (n = 12) and infliximab (n = 7). This might indicate incidences where the patient's entire treatment regime of biologics was claimed at one time, and not necessarily that more than one biologic immunomodulator was used at the same time (refer to Table A.22.2.2).

Tables 4.5.3.2 and 4.5.3.3 summarise the top ten pharmacological groups and top ten medicine items that were claimed in conjunction with biologic immunomodulators for RA patients during phase two of their treatment.

Table 4.5.3.2 indicates that the largest percentage of other medicine items that were claimed during phase two was again represented by the cytostatics, followed by corticosteroids, analgesics and COX-inhibitors.

According to Table 4.5.3.3, methotrexate was the most frequently claimed "other" medicine item (in combination with folic acid) during phase two, followed by the corticosteroid, prednisolone and the COX-2 inhibitors meloxicam and celecoxib. It was thus mostly methotrexate, corticosteroids like prednisone, and analgesics like the COX-2 inhibitors that were claimed as adjunctive therapy with biologic immunomodulators during phase two of RA treatment. The biphosphonate alendronate, which is indicated to treat various metabolic bone diseases as well as to prevent glucocorticoid-induced osteoporosis in postmenopausal women who do not receive estrogen (Snyman, 2010:84), was also claimed frequently (refer to Table 4.5.3.2).

Table 4.5.3.2 Top ten pharmacological groups claimed for RA patients during phase 2

Position	Pharmacological code	Description	Frequency	%n
1	23.1.1	Cytostatics	1,367	10.98
2	19.5.1	Corticosteroids	973	7.81
	8.6.1	Haematinics	808	6.49
3	3.3.1	Analgesics	503	4.04
4	4.1.1	COX-inhibitors	496	3.98
5	12.10.1	Gastro-intestinal tract	464	3.72
6	4.1.2	Selective COX-2 inhibitors	456	3.66
7	18.11.1	Antiprotozoal agents	439	3.52
8	12.4.4	Proton pump inhibitors	363	2.91
9	4.1.3	Specific cyclo-oxygenase-2 inhibitor	341	2.73
	40.1.1	*Unknown*	322	2.58
10	4.7.1	Biphosphonates	293	2.35
% n = frequency / 12446 **12446 = frequency of all the active ingredients claimed during phase 2**				

Table 4.5.3.3 Top ten active ingredients claimed for RA for patients during phase 2

Position	Pharmacological code	Active ingredient name	Description	Frequency	%n
1	23.1.1	Methotrexate	Cytostatics	1,367	10.98
	8.6.1	Folic acid	Haematinics	954	7.66
2	19.5.1	Prednisolone	Corticosteroids	680	5.46
3	4.1.2	Meloxicam	Selective COX-2 inhibitors	439	3.52
4	4.1.3	Celecoxib	Specific cyclo-oxygenase-2 inhibitor	425	3.41
5	19.3.1	Thyroxine	Thyroid agents	258	2.07
6	4.1.1	Diclofenac	COX-inhibitors	251	2.01
7	12.4.4	Omeprazole	Proton pump inhibitors	227	1.82
8	4.7.1	Alendronate	Biphosphonates	217	1.74
9	12.10.1	Sulphasalazine	Gastro-intestinal tract	211	1.69
10	7.7.2	Simvastatin	HMG-CoA reductase inhibitors	190	1.52
% n = frequency / 12446 **12446 = frequency of all the active ingredients claimed during phase 2**					

Other active ingredients (excluding those indicated to treat RA) also claimed frequently during phase two were the thyroid agent thyroxine, medicine items indicated for gastric ulcers (omeprazole) and medicine items indicated for cholesterol (simvastatin). The pharmacological group that was represented by the tenth largest percentage of active

ingredients was labelled as “unknown”, which is why the biphosphonates were selected as the tenth most prevalent pharmacological group. The “unknown” group on the database includes all new medicine items not yet classified, as well as unregistered and unscheduled medicine items.

Table A.22.2.1 in appendix B summarises the top ten combinations in which other medicine items were prescribed during phase two. As during phase one, most combinations prescribed during phase two of RA treatment included a DMARD (i.e. methotrexate, chloroquine, sulphasalazine), mostly in combination with a NSAID (i.e. meloxicam, aspirin, celecoxib, lumiracoxib, diclofenac, naproxen). Prednisolone was also frequently combined with a DMARD (and/or a NSAID). Again, in most cases where methotrexate was prescribed, folic acid was prescribed with it. According to the literature, it is good practice to prescribe these types on combinations during phase two of RA treatment. The literature indicates that the TNF-alpha inhibitors (i.e. etanercept, adalimumab and infliximab) should preferably be used in combination with methotrexate, and NSAIDs and corticosteroids may still be used to treat the symptoms of RA (refer to section 2.7.1.7).

Tables 4.5.4.1 and 4.5.4.2 summarise the top ten pharmacological groups and top ten medicine items claimed for RA patients during phase three of their treatment. This includes all the medicine items (excluding biologic immunomodulators) claimed for RA patients after treatment with biological medicine treatment had stopped.

Table 4.5.4.1 Top ten pharmacological groups claimed for RA patients during phase 3

Position	Pharmacological code	Description	Frequency	%n
1	19.5.1	Corticosteroids	365	7.29
2	23.1.1	Cytostatics	332	6.63
	40.1.1	*Unknown*	229	4.57
	8.6.1	Haematinics	208	4.15
3	4.1.3	Specific cyclo-oxygenase-2 inhibitor	182	3.63
4	4.7.1	Biphosphonates	169	3.37
5	12.4.4	Proton pump inhibitors	163	3.25
6	16.1.1	Diuretics	143	2.85
7	4.1.1	COX-inhibitors	143	2.85
8	3.1.1	Narcotic analgesics	138	2.75
9	19.6.2	Oestrogens	129	2.57
10	3.3.1	Combination analgesics	128	2.55
% n = frequency / 5001 **5001 = frequency of all the active ingredients claimed during phase 3**				

Table 4.5.4.1 indicates that after treatment with biologic immunomodulators had stopped, most of the medicine items claimed for RA patients were corticosteroids, followed by cytostatics. Other pharmacological groups with a high prevalence during phase three were the specific cyclo-oxygenase-2 inhibitors, biphosphonates and proton pump inhibitors. The only other pharmacological group indicated for RA that had a high prevalence during phase three was the COX-inhibitors.

According to Table 4.5.4.2, methotrexate was still the medicine item claimed the most after treatment with biologic immunomodulators had stopped, followed by prednisone. Other active ingredients with a high prevalence were celecoxib, and various other NSAIDs (meloxicam, diclofenac). DMARDs other than methotrexate also had a high prevalence, including leflunomide and sulphasalazine. Alendronate, pethidine and amitriptyline were the only other active ingredients (not indicated for RA) included in the top ten during phase three.

Table 4.5.4.2 Top ten active ingredients claimed for RA patients during phase 3

Position	Pharmacological code	Active ingredient name	Description	Frequency	%n
1	23.1.1	Methotrexate	Cytostatic	283	5.66
2	19.5.1	Prednisolone	Corticosteroid	260	5.20
	8.6.1	Folic acid	Haematinics	203	4.06
3	4.1.3	Celecoxib	Specific cyclo-oxygenase-2 inhibitor	173	3.46
4	4.7.1	Alendronate	Biphosphonates	148	2.96
5	4.1.2	Meloxicam	Selective COX-2 inhibitors	100	2.00
6	3.1.1	Pethidine	Narcotic analgesics	95	1.90
	40.1.1	*Unknown*	*Unknown*	93	1.86
7	12.10.1	Sulphasalazine	Gastro-intestinal tract	92	1.84
8	1.4.1	Amitriptyline	Tricyclic anti-depressants	90	1.80
9	4.6.1	Leflunomide	Musculo-skeletal agents (other)	89	1.78
10	4.1.1	Diclofenac	COX-inhibitors	75	1.50
% n = frequency / 5001 **5001 = frequency of all the active ingredients claimed during phase 3**					

Table A.22.3 shows the combinations in which the medicine items were claimed during phase three of RA treatment. When only two medicine items were prescribed together, it was mostly a medicine item indicated for pain and inflammation (i.e. a NSAID like celecoxib, diclofenac, and aspirin) and a corticosteroid (hydrocortisone, prednisone). Alendronate and calcium carbonate were also frequently combined, which according to the literature is

indicated to prevent bone loss and osteoporosis caused by long-term corticosteroid use (Rossiter, 2010:259). Corticosteroids were also often claimed in combination with a diuretic (bisoprolol, candesartan cilexetil), since chronic corticosteroid use may cause hypertension and edema (Rossiter, 2010:259). When more than two medicine items were combined during phase three of RA treatment, it was mostly a DMARD like methotrexate, sulphasalazine, chloroquine or leflunomide (most frequently methotrexate in combination with folic acid), together with another DMARD, and/or a corticosteroid (prednisolone), and/or an agent indicated to treat pain and inflammation (naproxen, celecoxib, diclofenac) (refer to Table A.22.3 in appendix B).

Figure 4.23 and Figure 4.24 illustrate how the percentages of the pharmacological groups and the medicine items changed during the three phases of RA treatment.

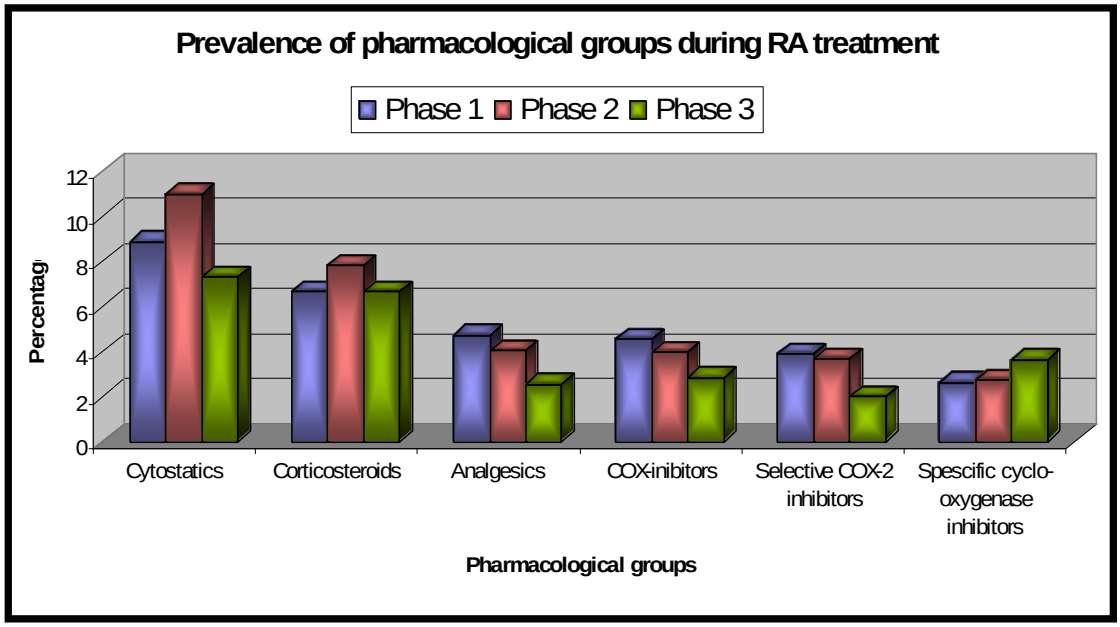

Figure 4.23 Percentages of pharmacological groups indicated for RA during each phase of the treatment

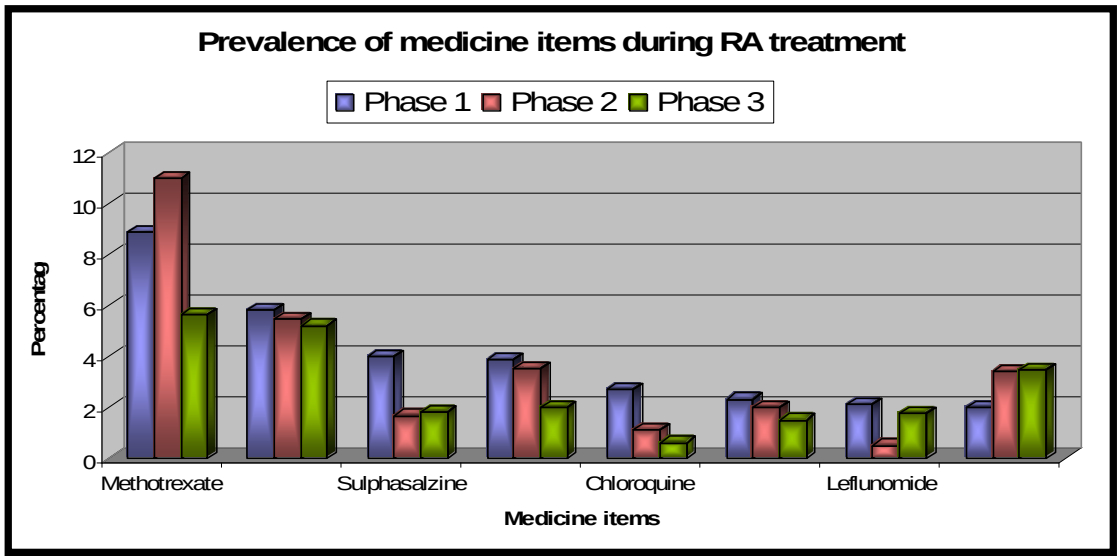

Figure 4.24 Percentages of active ingredients indicated for RA during each phase of the treatment

Figure 4.23 and Figure 4.24 indicates that the percentages represented by other RA medicine items decreased radically from before to after treatment with biologics. There was a significant decrease in the percentage of traditional DMARDs (i.e. methotrexate (cytostatics), sulphasalazine, chloroquine and leflunomide) from phase one to phase three, and the percentage of corticosteroids (i.e. prednisolone) also decreased considerably. There was also a noticeable decrease in the percentage of anti-inflammatory and pain medication (i.e. NSAIDs like meloxicam and diclofenac, and COX-2 inhibitors like celecoxib). This might be an indication that the use of biologic immunomodulators improved the disease prognoses of RA and caused a decrease in requirement of symptomatic treatments and other DMARDs, but the outcomes of medicine treatment were not measured in this study, and such a conclusion cannot necessarily be drawn. Furthermore, the composition of prescriptions claimed for RA patients was not investigated, which also limits the validity of this conclusion.

Section 4.4.1.2 indicated how the number of specific medicine items and pharmacological groups changed between the different phases of RA treatment between 2005 and 2008. The following sections will focus on the costs of all the medicine items and prescriptions (both biologic immunomodulators and other medication) claimed for RA patients during the four-year study period as well as the relevant changes that occured from one phase to the other. The frequencies of the medicine items and prescriptions claimed for RA patients during this period will also be investigated according to different demographic parameters (age, gender and prescriber type).

4.4.1.3 Number of medicine items and prescriptions claimed for RA patients

It was established from the analysis in section 4.4.1.1, that the number of the top ten medicine items claimed for RA patients decreased from before to after treatment with biologic immunomodulators. However, this does not indicate whether the total number of medicine items and prescriptions claimed for RA patients changed over the different phases. Table 4.5.5 (compiled from Tables A.23.1.1 to A.23.4 and A.24.1 to A.24.4) summarises the total number of medicine items and prescriptions claimed for RA patients according to age and gender.

Table 4.5.5 Number of medicine items and prescriptions claimed for RA patients

Number of items												
Phase		*Gender*		*Age group*				*Prescriber*				
	Total	*M*	*F*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	**17,550**	4,957	12,593	209	1,441	11,027	4,873	6,743	339	3,477	6,959	32
Phase 2	**15,011**	3,278	11,733	215	1,811	9,315	3,670	3,817	94	1,995	9,090	15
Biologics	2,565	668	1,897	61	414	1,599	491	170	0	125	2,268	2
Other	12,446	2,610	9,836	154	1,397	7,716	3,179	3,647	94	1,870	6,822	13
Phase 3	**5,001**	1,942	3,059	342	501	3,402	756	2,051	22	1,073	1,722	126
Number of prescriptions												
Phase		*Gender*		*Age group*				*Prescriber*				
	Total	*M*	*F*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	**6,271**	1,904	4,367	118	540	4,035	1,578	2,461	125	1,446	2,229	10
Phase 2	**7,131**	1,540	5,321	155	1,011	4,471	1,494	1,578	18	964	4,572	9
Biologics	2,480	645	1,835	61	379	1,564	476	158	0	118	2,202	2
Other	4,651	895	3,486	94	632	2,907	1,018	1,420	18	836	2,370	7
Phase 3	**2,120**	717	1,403	137	270	1,421	292	925	5	527	622	38

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Prescriber: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

Table 4.5.5 indicates that the total number of medicine items and prescriptions claimed for RA patients decreased from before to after treatment with biologic immunomodulators: the number of other medicines (excluding biologics) decreased by more than a factor of three from before (n = 17,550) to after (n = 5,001) treatment with biologic immunomodulators. The number of medicine items claimed during phase two (n = 15,011) was also smaller than the number claimed during the first phase of RA treatment, and the number of prescriptions decreased with 13% from phase one (n = 6,271) to phase three (n = 2,120) of RA treatment.

The largest percentage medicine items and prescriptions were claimed for female RA patients: between 60% and 70% of other medicine items (n = 12,593 *before* and n = 3,059 *after* treatment with biologics) and prescriptions (n = 4,367 *phase one*; n = 1,403 *phase three*) were claimed by females, and more than two thirds (about 74%) (n = 1,897) of all the RA biologic immunomodulators claimed during phase two were for female patients. This was, however, not unexpected, because most of the patients who received biologic immunomodulators were female (refer to section 4.4.1.1).

Furthermore, more than half (approximately 60%) of the total number of other medicine items (n = 11,027 *phase one* and n = 3,402 *phase three*) and prescriptions (n = 4,035 and n = 1,421 during *phase one* and *three* respectively) were claimed for patients in age group three (40 to 64 years), followed by approximately 26% (n = 4,873) of the medicine items and prescriptions (n = 1,578) claimed for patients older than 64 years of age. Less than 2% of the total number of other medicine items (n = 209 *phase one* and n = 342 *phase two*) and prescriptions (n = 118 *before* and n = 137 *after* treatment with biologics) were claimed for patients younger than 25 year of age. Of the biologic immunomodulators claimed for RA patients during phase two, more than two thirds (n = 1,599) were claimed for patients aged between 40 and 64 years, and only about 15% (n = 414) and 20% (n = 491) were claimed for patients in age groups two and four respectively. Biologic immunomodulators claimed for patients younger than 25 years represented only about 2% (n = 61) of all the biologic immunomodulators claimed for RA patients between 2005 and 2008. The frequency of medicine items and prescriptions claimed for each age group was also representative of the distribution of the patient population of RA (refer to section 4.4.1.1).

Furthermore, from Table 4.5.5 it is evident that the largest percentage of both other and biological medicine items and prescriptions claimed for RA patients were prescribed by either general practitioners, or specialists in prescriber group four, including among others, rheumatologists. Before treatment with biologic immunomodulators started, most of the prescriptions (39.24%) (n = 2,461) claimed were prescribed by general practitioners, whereas most of the medicine items (39.65%) (n = 6,959) were prescribed by specialists, which indicates that prescriptions prescribed by general practitioners during phase one of RA treatment, contained fewer medicine items per prescription (2.74 ± 2.23) than prescriptions prescribed by specialists (3.12 ± 2.45) during the same phase (refer to Tables A.25.1 and A.25.2 in appendix B).

During phase two, most of the biologic and other medicine items (n = 2,268) and prescriptions (n = 2,202) were prescribed by specialists: approximately 88% of all the biologic immunomodulators were prescribed by specialists in group four (i.e. rheumatologists

etc.), whereas only 6% (n = 170) were prescribed by general practitioners. No biologic immunomodulators were prescribed by neurologists, but there were two prescriptions with one item each prescribed by prescribers in group five (oncologists, radiotherapists etc.). A small percentage (about 5%) (n = 125) of biologic immunomodulators was prescribed by other prescribers (group three) (refer to Table 4.5.5). This is in line with the prescribing guidelines set by the SARAA, which state that biologics indicated for the treatment of RA must be prescribed by rheumatologists, or special permission should be obtained when other prescribers want to prescribe these agents (refer to section 2.7.1.7).

The average number of biologic immunomodulators per prescription was relatively similar when prescribed by a general practitioner (1.08 ± 0.37) or a specialist (1.03 ± 0.19) (refer to Table A.25.2 in appendix B). *(Tables A.25.1 and A.25.2 in appendix B shows how the average number of medicine items per prescription changed for different types of prescribers).*

On the other hand, after treatment with biologics had stopped (phase three), the largest percentage of medicine items and prescriptions claimed for RA patients were prescribed by general practitioners. Just over 40% (n = 925) of all medicine items (n = 5,001) and prescriptions (n = 2,120) claimed for RA patients during phase three of their treatment were prescribed by general practitioners, and only about 30% (n = 622) of all the prescriptions came from specialists. The number of prescriptions represented by specialists thus decreased from before (n = 2,229) to after (n = 622) treatment with biologic immunomodulators (refer to Table 4.5.5).

Section 4.4.1.4 discusses how the average number of medicine items per prescription per patient was influenced by treatment with biologic immunomodulators. Table 4.5.5 indicated that the number of medicine items and prescriptions claimed for RA patients decreased from before to after treatment with biologic immunomodulators.

4.4.1.4 Average number of medicine items per prescription per RA patient

Table 4.5.6 shows how the average number of medicine items per prescription per RA patient was influenced by biologic immunomodulators during the second phase of his/her treatment.

Table 4.5.6 Average number of medicine items per prescription per RA patient

Phase		*Average number of items/Rx*	*Average number of items/Rx: Gender*		*Average number of items/Rx: Age*			
			Male	*Female*	*Age group 1*	*Age group 2*	*Age group 3*	*Age group 4*
Phase 1		2.36 ± 1.48	2.68 ± 1.25	2.84 ± 1.05	1.97 ± 0.72	2.52 ± 0.76	2.79 ± 1.12	3.18 ± 1.25
Phase 2	***Biologics***	1.32 ± 1.33	1.59 ± 2.36	1.21 ± 0.44	1.08 ± 0.14	1.26 ± 0.55	1.37 ± 1.61	1.24 ± 0.43
	Other	2.81 ± 1.29	2.80 ± 1.44	2.81 ± 1.23	1.85 ± 0.26	2.50 ± 0.89	2.79 ± 1.33	3.22 ± 1.37
Phase 3		2.69 ± 1.61	2.99 ± 2.08	2.57 ± 1.36	1.76 ± 0.80	1.93 ± 0.98	2.79 ± 1.66	3.08 ± 1.73

According to Table 4.5.6, the average number of non-biologic medicine items per prescription claimed by an RA patient was usually not more than three, whereas the average number of biologic immunomodulators per prescription was seldom more than one (1.32 ± 1.33). Table 4.5.6 furthermore indicates that the average number of medicine items per prescription per patient claimed after treatment with biologic immunomodulators (2.69 ± 1.61) increased slightly from before treatment with biologic immunomodulators (2.36 ± 1.48). This increase was, however, not practically significant (*d*-value = 0.20). Thus, the total number of medicine items decreased from before to after treatment with biologics (refer to Table 4.5.5 and section 4.4.1.2), but the average number of medicine items per prescription increased, which may be an indication that the composition of the prescriptions changed from phase one to phase three.

Male and female patients with RA received approximately the same number of items per prescription (between two and three medicine items per prescription per patient). The average number of medicine items per prescription increased slightly for male RA patients (from 2.68 ± 1.25 to 2.99 ± 2.08) and decreased slightly for female RA patients from before (2.84 ± 1.05) to after (2.57 ± 1.36) treatment with biologic immunomodulators, but not significantly (*d*-value less than 0.2) (refer to Table 4..6).

When the average number of medicine items per prescription per patient is analysed according to different age groups, Table 4.5.6 indicates that before (3.18 ± 1.25) and after (3.08 ± 1.73) treatment with biologic immunomodulators, patients older than 39 years received more other medicine items (excluding biologics) per prescription per patient than patients younger than 40 years. Patients in age groups three and four received an average of three medicine items per prescription, whereas patients younger than 40 years (age groups one and two) received an average of two medicine items per prescription before and after treatment with biologic immunomodulators. After treatment with biologics, the average number of medicine items per prescription per patient decreased ever so slightly for all four

age groups, without the decrease being practically significant (*d*-value less than 0.2). The average number of biologic immunomodulators per prescription per patient was a little higher for RA patients in age group three (1.31 ± 1.61), but there was seldom more than one biologic immunomodulator per prescription for any patient of any age (refer to Table 4.5.6).

Table 4.5.6 thus indicates a insignificant increase in the average number of medicine items per prescription per patient from before to after treatment with biologics (*d*-value less than 0.2). Tables A.23.1 to A.23.4 and A.24.1 to A.24.4 in appendix B indicate whether and how the average cost per medicine item and the average cost per prescription claimed for RA patients between 2005 and 2008 changed from one phase of their treatment to the other.

4.4.1.5 Average cost per medicine item and prescription for RA patients per phase

According to Tables A.23.1.1 and A.24.1.1, the average cost of other medicine items before treatment with biologic immunomodulators was R128.45 ± 155.93 (median = R76.12), and the average cost per prescription was R359.49 ± 380.04 (median = R238.29).

As soon as RA patients started treatment with biologics, (phase two of RA treatment), the average cost per medicine item (R1477.88 ± 3134.39) and the average cost per prescription (R3110.98 ± 4146.23) increased with approximately 1000% and 700% respectively, but when the median is considered, it is evident that the cost of most medicine items (median = R105.23) and prescriptions (median = R440.18) only increased with 38.24% and 84.72% respectively. The reason for the considerable increase in the average costs might be ascribed to the fact that a number of biological medicine items were also claimed during phase two, and their sizeable costs influenced the average cost of medicine items and prescriptions noticeably. When the average cost of the therapies claimed during phase two is analysed according to “biologics” and “other medicine items” (excluding biologics) separately, this notion is confirmed: from Table A.23.1.2 it can be seen that the average cost per biologic immunomodulator (R8073.61 ± 2210.46) or a prescription that contained these medicine items (R8350.33 ± 2651.65) was practical significantly higher than the average cost of a other medicine items (R118.56 ± 168.24) (median = R75.33) or a prescription that only contained other medication (R327.27 ± 405.49) (median = R196.83) (*d*-value = 3.60 for biological medicine items and *d*-value = 3.03 for prescriptions).

The average cost of biologics was furthermore between 6185.17% and 3963.83% higher than the average cost of other medicines claimed before (phase one) and after (phase three) treatment with biologics respectively. After treatment with biologic immunomodulators, the

average cost of other medicine items (R198.67 ± 888.31) (median = R95.97) increased with 54.67% from before treatment with a biologic and the average cost of a prescription increased with 30.37% (refer to Table A.23.1.1 and A.23.1.2).

- *Average cost per medicine item and prescription for RA patients according to gender*

According to Tables A.23.1.1 and A.24.1.1, the average cost of other medicine items and prescriptions claimed before and during treatment with biologic immunomodulators was higher for male patients that for female patients. The average cost per other medicine item claimed for a male patient with RA during phase one was R140.38 ± 168.21 (median = R93.31), which was 13.43% higher than the average cost of a medicine item claimed for a female RA patient at R123.76 ± 150.57 (median = R71.81). The average cost per prescription claimed for a male RA patient during this phase was also 2.41% higher than the average cost per prescription claimed for a female patient with RA.

Tables A.23.2.2 and A.24.2.2 in appendix B indicate that the average cost per medicine item and prescription claimed during phase two of RA treatment was also higher for males than for females. The average cost of biologics was approximately 5% higher for males (average item cost of R8362.54 ± 2285.47 and average prescription cost of R8660.74 ± 2413.32) than for a female (average item cost of R7971.87 ± 1954.94 and average prescription cost of R8241.22 ± 2722.71).

After treatment with biologic immunomodulators however, the average cost per medicine item was 5.79% higher for female RA patients (R202.98 ± 1045.15) than for male RA patients (R191.87 ± 558.30), whereas the average cost per prescription was still 17.43% higher for males (R519.69 ± 1229.52) (median = R282.00) than for females (R442.56 ± 1726.04) (median = R179.32). However, when the median values of the cost of medicine items for females (median = R84.31) and males (median = R109.84) are taken into account, it is shown that most of the medicine items claimed for male RA patients did in fact have a higher cost than medicine items claimed for females patients. The higher average cost of medicine items for female RA patients could be explained by one or two outliers (i.e. female patients who received one or two relatively expensive medicine items or for whom more than one month's treatment was claimed at the same time) that influenced the average medicine item cost significantly.

Furthermore, the average cost of other medication (excluding biologics) increased for both male and female RA patients after treatment with biologics. The average cost per medicine

item increased with 36.68% and 64.01% for males and females respectively, whereas the average prescription cost for female RA patients increased with 24.01% from before to after treatment with biologics, while the average prescription cost for male RA patients increased with 42.19% during the same period. The difference in the average costs of medicine items and prescriptions between males and females was however not practically significant, as the *d*-values were less than 0.2 during each phase of the treatment (refer to Tables A.23.2.1 and A.24.2.1).

- *Average cost per medicine item and prescription for RA patients according to age*

When the average cost per medicine item and prescription is compared between the different age groups, Tables A.23.3.1 and A.24.3.1 in appendix B show that before treatment with biologics, the average cost per other medicine item and the average cost per prescription was the highest for patients between the ages of 40 and 64 years [R137.23 ± 163.05 (median = R87.72) and R375.03 ± 398.04 (median = R248.92) for medicine items and prescriptions respectively]. The average cost of medication was slightly less for medicine items [R115.54 ± 141.94 (median = R68.25), and relatively similar for prescriptions (R356.79 ± 351.98) (median = R249.99) claimed for patients older than 64 years. According to the average cost per medicine item (R110.13 ± 147.76) (median = R52.13) and the average cost per prescription (R293.87 ± 339.23) (median = R175.04), medication claimed for patients between 25 and 39 years was less than the average cost of medication claimed for patients older than 39 years, but the average cost of medicine items (R92.63 ± 86.26) (median = R75.27) and prescriptions (R164.06 ± 137.93) (median = R125.03) claimed for patients younger than 25 years was the lowest during phase one of RA treatment (refer to Tables A.23.3.1 and A.23.4.1). However, the median values show that most of the medicine items claimed for patients between 25 and 39 years had a lower cost (median = R52.13) than medicine items claimed for patients younger than 25 years (median = R75.27).

During phase two of RA treatment, the average cost of a biologic immunomodulator was the highest for patients older than 64 years (R8347.24 ± 1787.44). Next to age group four, biological medicine items claimed for patients in between the ages of 40 and 64 years had the highest average item cost (R8249.13 ± 2241.64). The average cost of a biologic immunomodulator was the lowest for patients between the ages of 25 and 39 years (R7036.27 ± 2226.98), which was about 19.91% less than the average cost of a biologic immunomodulator claimed for patients older than 64 years. The average cost per biological medicine item for patients younger than 25 years (R7586.36 ± 2273.98) was higher than the

average cost of biologics claimed by patients younger than 40, but less than the average cost of biologics claimed by patients older than 39 (refer to Tables A.23.3.2 and A.24.3.2).

The average cost of prescriptions that contained biologic immunomodulators did not differ significantly from the average cost of the individual biologic medicine items (refer to table A.24.3.2), because prescriptions for biologics rarely contained more than one medicine item per prescription (refer to Table 4.5.6) and thus display the same basic results for each age group as has been discussed above.

After treatment with biologics, the average cost of other medication increased for all patients except those in age group two, for whom the average medicine item cost (R101.01 ± 128.22) (median = R49.28) and average prescription cost (R187.42 ± 264.59) (median = R103.67) after treatment with biologics decreased with 9.03% and 56.80% respectively from before treatment with biologics. The average cost per medicine item for patients older than 39 years (age groups three and four) increased with 38.32% and 24.70% respectively, whereas the average cost per prescription for these two age groups increased with 21.18% and 4.55% respectively. The greatest increase in the average medicine treatment cost was for patients younger than 25 years, since the average cost of other medicine items (R550.37 ± 1110.69) (median = R166.03) and the average cost of other prescriptions (R1373.92 ± 2883.71) (median = R229.96) claimed for these patients after treatment with biologics were 494.16% and 285.08% higher than before treatment with biologics.

Thus, according to the average medicine item and prescription costs, the average cost per medicine treatment for patients younger than 25 years was more than 200% higher during phase three of RA treatment, than for patients older than 25 years (refer to Tables A.23.3.1 and A.24.3.1). However, the median values show that the increase in cost of most medicine items claimed for patients younger than 25 years was 120.58% from phase one (median = R75.27) to phase three (median = R166.03) and the cost of most prescriptions claimed for this group of patients increased with only 83.92% from before (median = R125.03) to after (median = R229.96) treatment with biologics. The difference in the average costs and the medians may be because one or two RA patients in age group one received one or two relatively expensive medicine items during phase three of their treatment, or more than one month's treatment was claimed as one prescription.

The *d*-values however indicate that the difference in the average cost of other medicines (excluding biologics) between the different age groups was not practically significant (*d*-values less than 0.2). Only during phase three was the impact of the high average cost of other medicine items and prescriptions claimed for patients younger than 25 years

considered to be medium (*d*-value = 0.4). On the other hand, the difference in the average cost per biologic immunomodulator between age groups four and two might be practically significant, as the *d*-value between these two costs was 0.63 (refer to Tables A.23.3.2 and A.24.3.2).

- *Average cost per medicine item and prescription for RA patients according to prescriber*

Table A.23.4.1 shows that before treatment with biologics, the average cost per medicine item was the highest for those items prescribed by neurologists (R237.69 ± 307.46) (median = R115.28), closely followed by the average cost of medicine items prescribed by specialists in group five (R212.73 ± 217.86) (median = R124.47), i.e. including oncologists and radiotherapists. The average cost of medicine items prescribed by specialists in group four (R135.66 ± 162.82) (median = R77.50), i.e. rheumatologists, was 56.81% less than those prescribed by specialists in group five, but 19.59% more than those prescribed by general practitioners (R113.44 ± 122.99) (median = R70.02). Medicine items prescribed by other prescribers (group three) had an average cost of R131.70 ± 170.14 (median = R79.56) relatively equal to those items prescribed by prescribers in group four. When the median values are, however, considered, it is shown that the cost of most prescriptions prescribed by specialists in group five (median = R124.47) was higher than the cost of most prescriptions prescribed by neurologists (median = R115.28).

Table A.24.4.1 shows essentially the same results for the average cost per prescription according to the different types of prescribers, except that the average cost per prescription prescribed by a specialist in group five (i.e. oncologists, etc.) was a little higher (R680.74 ± 475.49) than the average cost of a prescription prescribed by a neurologist (R644.58 ± 633.28). Thus, before treatment with biologic immunomodulators, the most costly medicine items and prescriptions were those prescribed by specialists like oncologists and radiotherapists and neurologists, followed by those prescribed by specialists like rheumatologists and endocrinologists. The least costly medicines were those prescribed by general practitioners.

After treatment with biologics (phases three), the average cost of medicine items and prescriptions prescribed by oncologists and other specialists in group five was approximately 300% higher than before treatment with biologics, and also significantly (between 170% and 500%) higher than the average cost of medicine items and prescriptions prescribed by prescribers in any other group. The average cost of medicine items prescribed by neurologists (R307.97 ± 429.16) (median = R118.86), general practitioners (R188.70 ±

501.90) (median = R101.75) and "other" prescribers (R221.79 ± 1633.83) (median = R95.54) also increased with 29.57%, 66.34% and 68.41% respectively from before treatment with biologics, whereas as the average cost per medicine item prescribed by rheumatologists and other specialists in group four stayed relatively the same (R136.82 ± 165.83) (median = R69.88). The increase in the average cost per prescription prescribed by neurologists was much more considerable than the increase in the average cost per item, since the average cost per prescription prescribed by neurologists (R1355.07 ± 1291.64) was 110.23% higher after treatment with biologics than before treatment with biologics. The average cost per prescription prescribed by other prescribers (group three) and general practitioners increased with 42.60% and 34.61% respectively from before treatment with biologic immunomodulators had started, and whereas the average cost per item prescribed by specialists in group four remained relatively the same from before to after treatment with biologics, the average cost per prescription of these prescribers decreased with 11.82% during the same period.

During phase three of RA treatment, there were also seven medicine items and three prescriptions prescribed by clinical hematologists, and for these the average cost per medicine item was R3049.75 ± 5349.33 and the average cost per prescription was R7116.08 ± 11717.32 (refer to Tables A.23.4.1 and A.24.4.1). The median values, however, show that the cost of most medicine items (median = R162.56) and prescriptions (median = R535.82) prescribed by clinical hematologists, was not much higher than the cost of most medicine items and prescriptions prescribed by the other prescribers (prescriber groups one to five). The high average cost of the medicine items and prescriptions might be ascribed to the possibility that one of the seven medicine items prescribed by clinical hematologists was relatively expensive, or that more than one month's medicine items were claimed simultaneously. Thus, after treatment with biologics, the average cost per medicine item and the average cost per prescription were the highest for those items prescribed by specialists in group five, and the lowest for those prescribed by specialists in group four and general practitioners (refer to Tables A.23.4.1 and A.24.4.1).

According to Table A.23.4.1, no RA biologics were prescribed by neurologists between 2005 and 2008. Only two biologic immunomodulators were prescribed by specialists in group five, and these had the highest average cost (R9828.00 ± 0.00). Most of the RA biologics were prescribed by specialists in group four (i.e. rheumatologists etc.), and biologic immunomodulators prescribed by this group of prescribers had a lower average cost (R8126.33 ± 2174.46) than the average cost of biologics prescribed by general practitioners (R8269.12 ± 2280.26). RA biologics prescribed by "other" prescribers (group three) had the lowest average cost (R6823.21 ± 2402.76). The average cost of biologic immunomodulators

prescribed to RA patients by specialists like rheumatologists was thus less than the average cost of biologic immunomodulators prescribed to RA patients by general practitioners (refer to Tables A.23.4.2 and A.24.4.2). The difference in the average cost of a biologic immunomodulator between the different types of prescribers was practically significant, since the *d*-values between the average item costs vary between 0.58 [between the two lowest costs (groups three and four)] and 1.25 [between the highest (group five) and lowest (group three) costs].

- *Summary of average cost per medicine item and prescription for RA patients per phase*

When the *d*-value is calculated between the average cost per medicine item claimed during phase two, and those claimed during phases one and three of RA treatment, a value of 0.4 is obtained. When the same is done for prescriptions claimed during the three phases, a value of 0.6 is obtained. According to this value, the impact of medicine items claimed during phase two was between "medium" and "large". However, when the *d*-value is calculated between the average cost of a biological medicine item or prescription claimed during this phase, and the cost of other medicine items (excluding biologics), the *d*-value is larger than 3 (3.6 and 3.0 respectively), which indicates that the size of the effect of biological therapy is large and practically significant (refer to Tables A.23.1.1 and A.24.1.1).

The analysis of the average medicine item cost and the average prescription cost thus indicates that a biologic immunomodulator or a prescription that contained biologic immunomodulators was relatively expensive. Since one of these prescriptions is so costly, it is important to determine the average number of biologic prescriptions that have been claimed for an RA patient over the four year study period. Table 4.5.7 (compiled from Tables A.26.1 to A.26.3 in appendix B) shows the average number of biologics prescription claimed per RA patient over the four-years from 2005 to 2008.

Table 4.5.7 Average number of biologic prescriptions per patient within the four-year study period

Average number of Rx per patient	***Average number of Rx/patient: Gender***		***Average number of Rx/patient: Age***			
	Male	*Female*	*Age group 1*	*Age group 2*	*Age group 3*	*Age group 4*
17.59 ± 12.84	15.73 ± 10.92	18.35 ± 13.53	15.25 ± 17.63	18.95 ± 16.15	17.00 ± 11.49	19.04 ± 14.48

According to Table 4.5.7, a patient with RA received an average of 17.59 ± 12.84 prescriptions for biologic immunomodulators over the four-year study period. Female patients received approximately three more biologics prescriptions over the four years than males, which was not practically significant (*d*-value = 0.19). When the average number of prescriptions per patient is analysed according to age, it is clear that RA patients between 25 and 39 years and patients older than 64 years received the most biologics prescriptions between 2005 and 2008, whereas patients younger than 25 years received the least biologics prescriptions per patient over the four years, but the difference was not practically significant (*d*-values approximately 0.2). It is clear form Table 4.5.7 that RA patients did not receive extraordinarily high numbers of prescriptions for biologic immunomodulators over the four-year period, but when the cost of these medicine products is taken into consideration, the total cost of treatment with biologic immunomodulators can amount to hundreds of thousands of rands for one patient. Section 4.4.1.6 indicates how the cost of biologic immunomodulators influences the total medicine treatment cost of RA.

4.4.1.6 Analysis of the total medicine treatment cost of RA per phase

Table 4.5.8 (compiled from Tables A.23.1.1 to A.23.4.2 and A.24.1.1 to A.24.4.2 in appendix B) summarises the total treatment cost of RA for each of the three phases of treatment between 2005 and 2008.

According to Table 4.5.8, biologic immunomodulators represented 0.28% (R20, 708,818.82) of the total cost (R7, 483,759,176.23) of all medication claimed through the PBM between 2005 and 2008. On the other hand, biologics represented 81.43% of the total medicine treatment cost (R25, 432,294.04) of RA during the four-year period. Other medication claimed before treatment with biologic immunomodulators represented 8.86% (R2, 254,330.44) of the total medicine treatment cost, whereas those claimed after treatment with biologic immunomodulators represented 3.91% (R993, 533.62).

The medicine treatment cost of RA was thus significantly higher during phase two of the treatment when patients received biologic immunomodulators. Biologics represented 93.35% of the total cost of medication (R22, 184,429.98) claimed during phase two, whereas other medication (excluding biologics) claimed during this phase only represented 6.65%. Furthermore, when the CPI of biologic immunomodulators is to be calculated, it is determined that biologics only represented 17.09% of the medicine items and 34.78% of the prescriptions claimed during phase two of RA treatment, but accounted for 93.35% of the total medication cost of that phase. When the percentage cost is divided by the percentage

frequency of the medicine items, a CPI of 5.46 is obtained, and when the percentage cost is divided by the percentage frequency of prescriptions, a CPI of 2.68 is obtained. Both these values further indicate how expensive these types of RA treatments are.

However, after treatment with biologics, the total medicine treatment cost of RA decreased with 126.90% from before treatment with biologics. This is most likely the result of the decrease in the total number of medicine items and prescriptions from phase one to phase three.

Table 4.5.8 furthermore shows that the medicine treatment cost for both male and female RA patients, as well as for the patients in all four age groups had the same trend as the total medicine treatment cost for the entire RA patient population. Table 4.5.8 however does indicate, that medication claimed for female RA patients contributed to about two thirds of the total medicine treatment cost during all three phases, whereas male RA patients represented less than 40%, which makes sense since most of the patients who received biologics were female and most of the medicine items and prescriptions that were claimed for RA patients between 2005 and 2008 were claimed for female patients.

It is also indicated that patients in age group three contributed to almost two thirds of the total medicine treatment cost of each phase, which means that the largest percentage of the total medicine treatment cost of RA was spent on patients between the ages of 40 and 64 years. This was also expected since patients in age group three represented the largest percentage of patients with RA and the largest percentage of medicine items and prescriptions was also claimed for this age group (refer to Table 4.5.8).

Table 4.5.8 Total medicine treatment cost of RA per phase

	Total medicine treatment cost												
Phase	**Variables**		***Gender***		***Age group***				***Prescriber***				
		Total	*Males*	*Females*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	Total	**2,254,330.44**	695,871.33	1,558,459.11	19,359.05	158,690.67	1,513,263.24	563,017.48	764,948.82	80,572.97	457,914.48	944,086.73	6,807.44
	Scheme	1,833,469.09	568,952.30	1,264,516.79	14,163.98	139,113.42	1,251,747.50	428,444.19	614,873.38	66,342.45	369,410.27	777,169.46	5,673.53
	Patient	420,861.35	126,919.03	293,942.32	5,195.07	19,577.25	261,515.74	134,573.29	150,075.44	14,230.52	88,504.21	166,917.27	1,133.91
Phase 2	Total	**22,184,429.98**	5,937,684.03	16,246,745.95	475,807.33	3,100,911.59	14,118,352.00	4,489,359.06	1,809,347.24	8,946.91	1,065,898.39	19,279,275.36	20,962.08
	Scheme	21,161,818.13	5,617,147.85	15,544,670.28	473,686.50	2,803,955.16	13,630,473.61	4,253,702.86	1,658,592.50	5,457.27	983,431.49	18,493,379.46	20,957.41
	Patient	1,022,611.85	320,536.18	702,075.67	2,120.83	296,956.43	487,878.39	235,656.20	150,754.74	3,489.64	82,466.90	785,895.90	4.67
Biologics	Total	**20,708,818.86**	5,586,176.58	15,122,642.28	462,768.07	2,913,014.56	13,190,351.27	4,142,684.96	1,405,750.01	0.00	852,900.86	18,430,511.99	19,656.00
	Scheme	19,970,653.39	5,336,573.48	14,634,079.91	462,768.07	2,635,834.00	12,877,440.28	3,994,611.04	1,348,640.91	0.00	807,944.85	17,794,411.63	19,656.00
	Patient	738,165.47	249,603.10	488,562.37	0.00	277,180.56	321,910.99	148,073.92	57,109.10	0.00	44,956.01	636,100.36	0.00
Other	Total	**1,475,611.12**	351,507.45	1,124,103.67	13,039.26	187,897.03	928,000.73	346,674.10	403,597.23	8,946.91	212,997.53	848,763.37	1,306.08
	Scheme	1,191,164.74	280,574.37	910,590.37	10,918.43	168,121.16	753,033.33	259,091.82	309,951.59	5457.27	175,486.64	698,967.83	1,301.41
	Patient	284,446.38	70,933.08	213,513.30	2,120.83	19,775.87	174,967.40	87,582.28	93,645.64	3,489.64	37,510.89	149,795.54	4.67
Phase 3	Total	**993,533.62**	372,619.35	620,914.27	188,226.72	50,604.74	645,778.67	108,923.49	387,018.14	6,775.35	237,982.00	235,609.22	104,800.66
	Scheme	776,761.35	310,321.72	466,439.63	15,172.97	38,298.86	500,125.93	86,163.59	311,255.60	6,348.83	155,343.07	196,722.53	85,914.54
	Patient	216,772.27	62,297.63	154,474.64	36,053.75	12,305.88	145,652.74	22,759.90	75,762.54	426.52	82,638.93	38,886.69	18,886.12

When the medicine treatment cost is analysed according to prescriber type, it is clear that more than 60% of the total medicine treatment cost of each phase of RA treatment went towards medication prescribed by either general practitioners or specialists is group four (i.e. rheumatologists). Before treatment with biologics, medication prescribed by specialists contributed 42% of the total medicine treatment cost, and those prescribed by general practitioners contributed 33.93%. During phase two, biologic immunomodulators prescribed by specialists represented 89.00% of the total cost of biologics, and those biologic immunomodulators prescribed by general practitioners represented 6.79%. The remaining 4.21% was represented by specialists in group five (i.e. oncologists, radiotherapists etc.) and "other" prescribers in group three. The largest percentage (57.52%) of the cost of other medication (excluding biologics) also prescribed during phase two, was also represented by specialists in group four, followed by the cost of medication prescribed by general practitioners, which represented 27.35% of the total medication cost of non-biologic medicines prescribed during phase two. After treatment with biologics, however, the largest percentage (38.95%) of the total medication cost was spent on prescriptions from general practitioners, and not specialists (23.71%) (refer to Table 4.5.8).

Thus, from Table 4.5.8 it can be seen that not only did the total medicine treatment cost of RA decrease from before to after treatment with biologic immunomodulators, but the expenditure on specialists like rheumatologists also decreased after treatment with biologics.

The data discussed in sections 4.4.1.5 and 4.4.1.6 showed that the average cost per medicine item and the average cost per prescription increased for RA patients from before to after treatment with biologics, but that the total medicine treatment cost of RA decreased from phase one to phase three. However, as discussed in chapter three, the method by which the average cost per medicine item and prescription is calculated does not take into consideration the variations between individual patients. The *average cost per item per patient* as well as the *average cost per prescription per patient* on the other hand, does take variations between individual patients into account. The average cost per medicine item per patient and the average cost per prescription per patient will therefore also be discussed in order to determine whether there is a difference between the average cost per item (or prescription) and the average cost per item (or prescription) *per patient*.

4.4.1.7 Average cost per medicine item per RA patient and the average cost per prescription per RA patient

Table 4.5.9 summarises the average cost per medicine item per patient and the average cost per prescription per patient across the four-year period between 2005 and 2008.

According to Table 4.5.9, there were 141 patients with RA who received biologic immunomodulators between 2005 and 2008. Of these patients, 130 (92.20%) received other medication before starting treatment with biologics, and 129 (91.49%) received other medicines (excluding biologics) during the same period they received treatment with biologic immunomodulators. After treatment with biologics, 104 (73.76%) RA patients continued treatment with other medicine items.

This might indicate that eleven RA patients either passed over the first steps of the treatment protocol, or only joined a medical aid scheme when they started using biologic immunomodulators, and that 37 of the RA patients either no longer received other medication after they had received treatment with biologics, or left the medical aid scheme after treatment with biologic immunomodulators had stopped.

Table 4.5.9 Average cost per medicine item and prescription per RA patient

Average cost per medicine item per patient					
Phase		*Patients*	*Total item cost*	*Medical aid scheme*	*Levy*
Phase 1		130	133.21 ± 64.19	112.25 ± 59.71	20.96 ± 19.99
Phase 2	*Biologics*	141	8364.15 ± 1991.67	7921.01 ± 2142.95	443.13 ± 1565.78
	Other	129	113.58 ± 56.36	90.69 ± 49.71	22.89 ± 21.32
Phase 3		104	149.27 ± 141.46	106.19 ± 91.49	43.08 ± 80.02
Average cost per prescription per patient					
Phase		*Patients*	*Total item cost*	*Medical aid scheme*	*Levy*
Phase 1		130	139.17 ± 67.21	117.72 ± 61.59	21.45 ± 20.46
Phase 2	*Biologics*	141	8364.15 ± 1991.67	7921.01 ± 2142.95	443.13 ± 1565.78
	Other	129	116.66 ± 61.71	93.41 ± 54.46	23.25 ± 21.57
Phase 3		104	155.12 ± 166.71	110.95 ± 120.74	44.17 ± 80.58

Table 4.5.9 furthermore shows that the average cost per medicine item per patient claimed during phase one of RA treatment was R133.21 ± 64.19. The average cost per prescription

per patient claimed during this phase of RA treatment was only about R6.00 more (R139.17 ± 67.21).

During phase one of RA treatment, the medical aid scheme paid approximately 84% of the total medicine cost and the patient co-paid 16%. The average cost of other medicine items per patient (R133.21 ± 64.19) and the average cost per other prescription per patient (R139.17 ± 67.21) decreased with 19.30% from phase one of RA treatment to phase two (R113.58 ± 56.36 for medicine items) and (R116.66 ± 61.71 for prescriptions), but the average cost per biologic immunomodulator (R8364.15 ± 1991.67) was significantly higher (7069.68%) than the average cost of other treatments claimed during the same period, which increased the average medicine treatment cost per patient during phase two of RA treatment considerably (refer to Table 4.5.9).

Furthermore, during phase two of RA treatment, the medical aid scheme paid 80.07% of the total medicine cost of other therapies, but 94.69% of the final cost of biological therapies. Even though the patient only paid about 6% of the final cost of biological medicine items and prescriptions, the average patient levy per RA patient could still get relatively high (R443.13 ± 1565.78), even though most patients did not pay a levy (median = R0.00). After treatment with biologics, the average cost per medicine item per patient (R149.27 ± 141.46) and the average cost per prescription per patient (R155.12 ± 166.71) (median = R120.96) increased with approximately 12% from before treatment with biologics. During this phase of RA treatment the medical aid scheme's contribution to the final medicine cost was only 71% and the patient co-paid 29%. Together with a higher percentage contribution to the final cost of medicines, the average amount co-paid per patient increased with 106% from before to after treatment with biologics, whereas the average amount paid by the medical aid scheme decreased with 6.10% (refer to Table 4.5.9).

Thus, the analysis of the average cost per medicine item and prescription *per treatment phase* of RA, and the average cost per medicine item and prescription *per RA patient* shows the same trend: the average cost per medicine item and average cost per prescription increased between 2005 and 2008, but, according to Table 4.5.8, the total medicine treatment cost of RA patients decreased from before to after treatment with biologic immunomodulators (between 2005 and 2008).

4.4.1.8 Summary of analysis of patients with rheumatoid arthritis

Between 2005 and 2008, there were 141 patients with RA who claimed the biologic immunomodulators indicated for this disease (i.e. etanercept, adalimumab, infliximab and rituximab) through the PBM. These patients represented 19.78% of the total number of patients (n = 713) (refer to Figure 3.1) on the PBM database who claimed biologics during the four-year period. The ratio of females to males with RA was more than two to one (2.44:1), and more than 80% of the RA patients were older than 39 years of age, of which the most were between the ages of 40 and 64 years. This distribution of RA patients according to age and gender is in exact accordance with what is stated in the literature (refer to section 2.7.1.2 in chapter 2).

The average cost per medicine item and the average cost per prescription as claimed by RA patients between 2005 and 2008 increased from before treatment with biological medicine, to after. This increase was, however, not unexpected, since the average costs of all the medicine items and prescriptions claimed through the total PBM database also increased between 2005 and 2008. The increase in the average cost of medication can be ascribed to, amongst other, an increase in medical inflation and the consumer price index.

On the other, the total number of medicine items and prescriptions claimed by RA patients between 2005 and 2008 decreased significantly from before treatment with biologic immunomodulators to after treatment with these agents, which could be ascribed to the decrease in the number of RA patients from phase one to phase three (refer to Table 4.5.9). Therefore, even though the average cost per medicine item and prescription increased the total treatment cost of RA decreased considerably from before to after treatment with biologics.

Despite the fact that biologic immunomodulators for the treatment of RA are relatively expensive and would cost both the third party payers (medical aid schemes) and the patients who utilise them considerable amounts of money, it does appear to decrease the cost of other medication used by these patients, which might benefit both the medical aid schemes and the patients in the long run. However, treatment outcomes were not measured in this study and the impact of biological therapies on RA patients' disease progress was not established. Furthermore, the composition of prescriptions claimed for RA patients before and after treatment with biologics was also not investigated, and therefore it was difficult to establish exactly why the number of medicine items and prescriptions claimed for RA patients decreased from phase one to phase three of their treatment.

4.4.2 Analysis of patients with Multiple Sclerosis (MS)

The patients included in this section's analysis are all the patients who received at least one prescription for either interferon beta-1a or interferon beta-1b between 2005 and 2008, who had at least two positive diagnostic codes for multiple sclerosis (i.e. ICD-10 MPA code: G35, diagnosed code: MSS, ICD-10 claim code: MSS).

4.4.2.1 Number of MS patients on the database between 2005 and 2008

This section first indicates how many patients with MS received biologic immunomodulators between 2005 and 2008. The total number of MS patients by whom interferons were claimed through the PBM during the study period is summarised in Table 4.6.1 (summarised from Tables A.31.1 to A.31.3 in appendix B) according to gender and age.

Table 4.6.1 Number of MS patients on the database between 2005 and 2008

Total number of patients	Number of patients according to gender		Number of patients according to age group			
172	***Male***	***Female***	***AG 1***	***AG 2***	***AG 3***	***AG 4***
	29	143	11	50	106	5

Table 4.6.1 shows that there were 172 patients with MS who received biologic immunomodulators during the four-year period, and of these 29 were male and 143 were female. Thus, 83.14% of all the patients diagnosed with MS between 2005 and 2008 were female, whereas only 16.86% were male, giving a ratio of males to females as 1:4.93. Most of the patients (61.63%) diagnosed with MS were between the ages of 40 and 64 years, whereas the second largest percentage (29.07%) of MS patients was between the ages of 25 and 39 years of age. Less than 7% of all the patients with MS were younger than 25 years, and only about 2% were older than 64 years. According to Beers (2006:1888), the peak onset of MS is often between 20 and 40 years, but ranges from 15 to 60 years. The literature furthermore states that women are more often affected by MS than men. The distribution of the patient population of the database with MS is thus relatively in line with the literature.

4.4.2.2 Top ten medicine items and pharmacological groups claimed for MS patients during each phase

In this section, the top ten active ingredients as well as the top ten pharmacological groups were compiled for each of the three phases of MS treatment between 2005 and 2008.

Tables 4.6.2.1 and 4.6.2.2 summarise the top ten pharmacological groups and top ten active ingredients claimed for MS patients during phase one of their treatment. This includes all the medicine items (excluding biologic immunomodulators) claimed for MS patients before starting with biological medicine treatment.

Table 4.6.2.1 indicates that most of the active ingredients that were claimed during phase one of MS treatment, were SSRIs. This was followed by combination analgesics and corticosteroids. Anti-epileptics, tricyclic antidepressants and benzodiazepines also had a high prevalence of use during phase one of MS treatment.

Table 4.6.2.1 Top ten pharmacological groups claimed for MS patients during phase 1

Position	Pharmacological code	Description	Frequency	% n
1	1.4.4	Selective serotonin re-uptake inhibitors	446	7.23
2	3.3.1	Combination analgesics	301	4.88
	40.1.1	Unknown	226	3.66
3	19.5.1	Corticosteroids	221	3.58
4	1.6.1	Anti-epileptics	219	3.55
5	7.3.8	ACE inhibitors	217	3.52
6	1.4.1	Tricyclic antidepressants	198	3.21
7	4.1.1	COX inhibitors	185	3.00
8	1.3.1	Benzodiazepines	172	2.79
9	1.2.3	Sedative hypnotics (other)	158	2.56
10	12.4.4	Proton pump inhibitors	133	2.16
% n = frequency / 6171 **6171 = frequency of all the active ingredients claimed during phase 1**				

All of these pharmacological groups are used as symptomatic therapies for MS before treatment with biologic immunomodulators start (refer to Table 2.16): SSRIs are the treatment of choice for MS associated depression, although tricyclic antidepressants are also indicated, whereas anti-epileptics (i.e. gabapentin, carbamazepine) and benzodiazepines

(diazepam, alprazolam) are indicated to treat spasticity associated with MS (Calabresi, 2004:1939; Longmore *et al*., 2007:488) (refer to Table 2.16 in chapter 2).

Table 4.6.2.2 Top ten active ingredients claimed for MS patients during phase 1

Position	Pharmacological code	Active ingredient	Description	Frequency	% n
1	19.5.1	Prednisolone	Corticosteroids	147	2.38
2	1.4.1	Amitriptyline	Tricyclic antidepressants	143	2.32
3	1.4.4	Fluoxetine	Selective serotonin re-uptake inhibitors	140	2.27
4	1.4.4	Citalopram	Selective serotonin re-uptake inhibitors	138	2.24
5	19.3.1	Thyroxine	Thyroid agents	111	1.80
6	1.4.4	Escitalopram	Selective serotonin re-uptake inhibitors	109	1.77
7	1.2.3	Zolpidem	Sedative hypnotics (other)	104	1.69
8	1.3.1	Alprazolam	Benzodiazepines	102	1.65
9	3.3.1	Par/Cod/Caff/Mepro	Combination analgesics	97	1.57
10	7.3.8	Lisinopril	ACE inhibitors	88	1.43
% n = frequency / 6171 **6171 = frequency of all the active ingredients claimed during phase 1**					

According to Table 4.6.2.2, the medicine items indicated for the depression associated with MS were most frequently claimed: the tricyclic antidepressant amitriptyline, and the SSRIs fluoxetine, citalopram, and escitalopram. Prednisolone, which is indicated to treat an acute relapse of MS, was the single medicine item with the highest frequency, and the benzodiazepine derivate zolpidem, and the benzodiazepine alprazolam used for spasticity were also claimed at high frequencies.

The top ten combinations in which the medicine items were claimed during phase one of MS treatment are summarised in Table A.27.1 in appendix B. The medicine items indicated for MS most frequently claimed in combination with each other were those indicated for MS associated depression (i.e. SSRIs such as citalopram, escitalopram, fluoxetine and sertraline or tricyclic anti-depressants such as amitriptyline and imipramine) together with agents indicated for pain and spasticity (i.e. baclofen, anti-epileptics like gabapentin, lamotrigine, valproate or benzodiazepines such as alprazolam) , and/or something to treat MS associated bladder urgency (oxybutynin). Amantadine and zolpidem (indicated for MS associated fatigue) were also frequently claimed in combination with medicine items indicated for depression and pain (refer to Table A.27.1 in appendix B).

Tables 4.6.3.1 to 4.6.3.3 show which medicine items were most frequently claimed for MS patients during phase two of their treatment. Phase two is considered as that period in which a patient with MS received either interferon beta-1a or interferon beta-1b. Table 4.6.3.1 indicates the frequencies at which these two biologic immunomodulators were claimed for patients during phase two of their treatment.

Table 4.6.3.1 Biologic immunomodulators claimed for MS patients during phase 2

Position	Pharmacological code	Active ingredient name	Description	Frequency	%n
1	24.2.1	Interferon beta-1a	Immunostimulants	2,466	24.14%
2	24.2.1	Interferon beta-1b	Immunostimulants	1,640	16.05%
% n = frequency / 10215 **10215 = frequency of all the active ingredients prescribed claimed phase 2**					

Interferon beta-1a and interferon beta-1b represented 40.20% of all the medicine items claimed for MS patients during phase two of their treatment. Interferon beta-1a represented 24.14% of all the medicine items claimed for MS patients during phase two, whereas interferon beta-1b represented only 16.05% of all the medicine items claimed during this phase of MS treatment. Interferon beta-a represented 60.06% of all the biologic immunomodulators claimed during this phase of MS treatment, whereas interferon beta-1b represented the remaining 39.94%. Interferon beta-1a was thus claimed more frequently (almost twice as often) than interferon beta-1b to treat MS.

According to Table A.27.2.2 in appendix B, interferon beta-1a and interferon beta-1b were mostly claimed as single biological medicine item per prescription. When biologic immunomodulators claimed for MS patients were, however, combined, it was mostly interferon beta-1a that was claimed in combination with another medicine item that contained interferon beta-1a per prescription (i.e. more than one biological medicine item per prescription).

Tables 4.6.3.2 and 4.6.3.3 summarise the top ten pharmacological groups and top ten medicine items claimed for MS patients during phase two of their treatment. This includes all the medicine items (excluding biologic immunomodulators) claimed for MS patients during the period they received biological medicine treatment.

Table 4.6.3.2 Top ten pharmacological groups claimed for MS patients during phase 2

Position	Pharmacological code	Description	Frequency	%n
1	1.6.1	Anti-epileptics	873	8.55
2	1.4.4	Selective serotonin re-uptake inhibitors	772	7.56
3	3.3.1	Combination analgesics	430	4.21
4	1.4.1	Tricyclic antidepressants	411	4.02
5	5.4.1	Anticholinergics	360	3.52
6	1.2.3	Sedative hypnotics (other)	346	3.39
7	19.3.1	Thyroid agents	317	3.10
	40.1.1	Unknown	310	3.03
8	1.3.1	Benzodiazepines	288	2.82
9	7.3.8	ACE inhibitors	269	2.63
10	4.5.1	Centrally acting muscle relaxants	259	2.54
% n = frequency / 10215 **10215 = frequency of all the active ingredients claimed during phase 2**				

Most of the medicine items that were claimed as adjunctive therapy with interferon beta during phase two of MS treatment were anti-epileptic agents, followed by SSRIs. Other pharmacological groups also frequently claimed were combination analgesics, tricyclic antidepressants, anticholinergics and sedative hypnotics. Table 4.6.3.3 shows what medicine items of these pharmacological groups were claimed most frequently.

Table 4.6.3.3 Top ten active ingredients claimed for MS patients during phase 2

Position	Pharmacological code	Active ingredient	Description	Frequency	%n
1	1.4.1	Amitriptyline	Tricyclic antidepressants	331	3.24
2	19.3.1	Thyroxine	Thyroid agents	307	3.01
3	1.2.3	Zolpidem	Sedative hypnotics (other)	258	2.53
4	1.4.4	Fluoxetine	Selective serotonin re-uptake inhibitors	244	2.39
5	5.4.1	Oxybutynin	Anticholinergics	244	2.39
6	1.4.4	Escitalopram	Selective serotonin re-uptake inhibitors	227	2.22
7	4.5.1	Baclofen	Centrally acting muscle relaxants	215	2.10
8	1.6.1	Gabapentin	Anti-epileptics	189	1.85
9	1.6.1	Clonazepam	Anti-epileptics	169	1.65
	40.1.1	Unknown	New product	168	1.64
10	1.6.1	Lamotrigine	Anti-epileptics	165	1.62
% n = frequency / 10215 **10215 = frequency of all the active ingredients claimed during phase 2**					

Based on Table 4.6.3.3, the medicine items claimed most frequently in addition to biologic immunomodulators during phase two of MS treatment were amitriptyline, thyroxine, zolpidem, fluoxetine, oxybutynin and escitalopram. Except for thyroxine (which is a thyroid hormone used to treat hypothyroidism), the medicine items in the top six are all indicated to treat symptoms of MS. The first three are used as treatment for MS associated depression, whereas oxybutynin is indicated to treat bladder urgency also associated with MS. Escitalopram is also used to treat MS associated depression. The rest of the top ten medicine items are all used to treat spasticity as well as pain and paroxymal symptoms associated with MS (Calabresi, 2004:1939; Longmore *et al*., 2007:488) (refer to Table 2.16 in chapter 2). It is thus evident that it was the medicine items indicated for treating the symptoms of depression, spasticity and pain, that were used in conjunction with biologics during phase two of MS treatment (refer to Table 4.6.3.3). This might be ascribed to the fact that beta interferons are known to cause depression and flu-like symptoms (i.e. pain, headache etc.) as side-effects (Serono, Inc., 2003) (refer to Table 2.18).

Table A.27.2.1 in appendix B shows how these items were combined with each other during phase two. Prescriptions with more than one medicine item usually combined one or more of the medicine items for pain and spasticity (baclofen, tramadol, valproic acid, lamotrigine, clonazepam, topiramate, gabapentin, oxcarbazepine, carbamazepine, alprazolam, lorazepam, temazepam) with one or more of the medicine items for depression (escitalopram, amitriptyline, fluoxetine, sertraline, venlafaxine, fluvoxamine, paroxetine and imipramine). According to the literature, the first component of MS treatment is to relieve the symptoms of the disease, which mostly involve spasticity, pain, depression, bladder urgency and fatigue (refer to Table 2.16). Since these symptoms often present together, it is necessary to combine medicine groups to treat all the symptoms that a patient presents with. The medicine combinations shown in Table A.27.2.1 is thus in line with the treatment protocols as stated in the literature.

Tables 4.6.4.1 and 4.6.4.2 summarise the top ten pharmacological groups and top ten medicine items claimed for MS patients during phase three of their treatment. These include all the medicine items (excluding biologic immunomodulators) claimed for MS patients after treatment with biological medicine treatment had stopped.

Table 4.6.4.1 Top ten pharmacological groups claimed for MS patients during phase 3

Position	Pharmacological code	Description	Frequency	%n
1	1.6.1	Anti-epileptics	196	8.77
2	1.4.4	Selective serotonin re-uptake inhibitors	180	8.06
3	5.4.1	Anticholinergics	121	5.42
4	3.3.1	Combination analgesics	86	3.85
5	4.5.1	Centrally acting muscle relaxants	84	3.76
6	4.1.1	COX inhibitors	69	3.09
7	1.2.3	Sedative hypnotics (other)	67	3.00
8	1.3.1	Benzodiazepines	59	2.64
9	19.3.1	Thyroid agents	58	2.60
10	7.7.2	HMG-CoA reductase inhibitors	58	2.60
% n = frequency / 2234 **2234 = frequency of all the active ingredients claimed during phase 3**				

Table 4.6.4.1 shows that the top pharmacological groups represented by the medicine items claimed for MS patients during phase three of their treatment did not change much after treatment with biologic immunomodulators had stopped. It was still the anti-epileptics, SSRIs and anticholinergics that were claimed most frequently. Table 4.6.4.2 shows that of these pharmacological groups, it was mostly citalopram (indicated for depression), baclofen (indicated for pain and spasticity) and tolteradine (indicated for bladder urgency) that were claimed for MS patients during phase three of their treatment.

Table 4.6.4.2 Top ten active ingredients claimed for MS patients during phase 3

Position	Pharmacological code	Active ingredient	Description	Frequency	%n
1	1.4.4	Citalopram	Selective serotonin re-uptake inhibitors	71	3.18
2	4.5.1	Baclofen	Centrally acting muscle relaxants	69	3.09
3	5.4.1	Tolteradine	Anticholinergics	65	2.91
4	1.6.1	Gabapentin	Anti-epileptics	46	2.06
5	20.4.1	Potassium chloride	Minerals and electrolytes	44	1.97
6	1.4.5	Duloxetine HCl	Seretonin & noradrenaline re-uptake inhibitors	42	1.88
7	1.2.3	Zolpidem	Sedative hypnotics (other)	41	1.84
8	4.1.1	Ibuprofen	COX inhibitors	40	1.79
9	1.4.1	Amitriptyline	Tricyclic antidepressants	38	1.70
10	5.4.1	Oxybutynin	Anticholinergics	39	1.75
% n = frequency / 2234 **2234 = frequency of all the active ingredients claimed during phase 3**					

Tables 4.6.4.1 and 4.6.4.2 also showed that the frequencies the medicine items indicated to treat (among others) MS were claimed, decreased rather significantly after MS patients had been treated with biologic immunomodulators, which allowed for some non-MS therapies (thyroid agents and cholesterol agents) to be included in the top ten.

Table A.27.3 in appendix B furthermore shows that the frequency of combination prescriptions decreased between phase one and phase three of MS treatment. There were only seven combinations with more than two medicine items per prescription at a frequency higher than one during phase three, and only six combinations with more than three medicine items per prescription. It is also evident from Table A.27.3 that the top ten combination prescriptions with two, three and four medicine items respectively, did not merely include those with medicine items indicated for MS.

The use of medicine items to treat pain and spasticity (especially anti-epileptics) in combinations with other symptomatic treatments also decreased significantly (refer to Table A.27.3). Figure 4.25 and Figure 4.26 illustrate how the percentages of the pharmacological groups and the medicine items changed during the three phases of MS treatment.

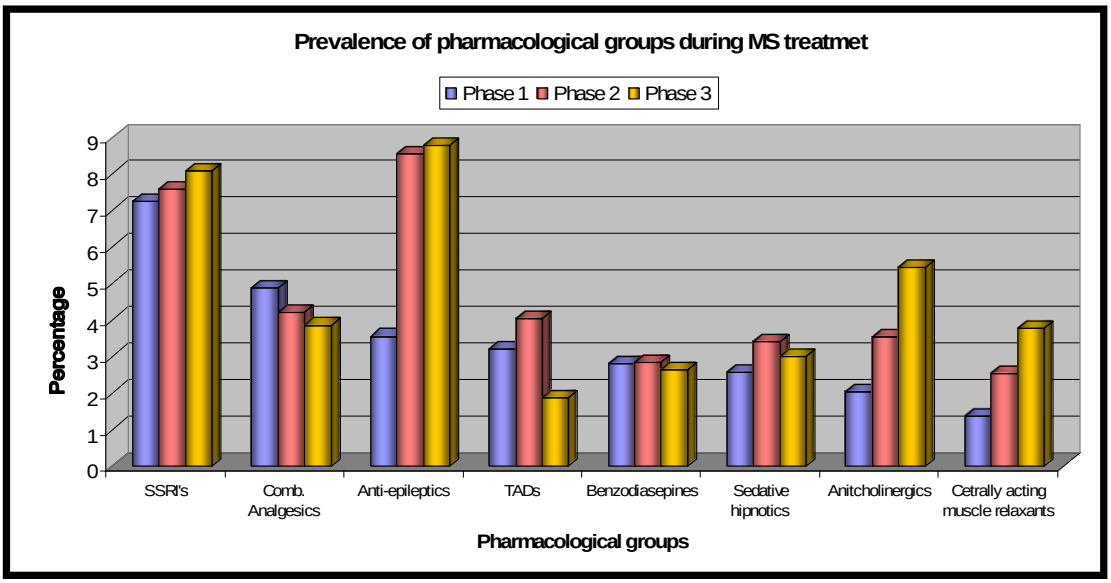

Figure 4.25 Percentages of pharmacological groups indicated for MS during each phase of the treatment

Figure 4.25 indicates that the percentages of the pharmacological groups into which the symptomatic treatments of MS are divided, decreased from before to after treatment with biologic immunomodulators. On the other hand, the percentages of these pharmacological groups increased during phase two of MS treatment. Figure 4.26 shows how the individual

medicine items included in these pharmacological groups changed over the course of their treatment.

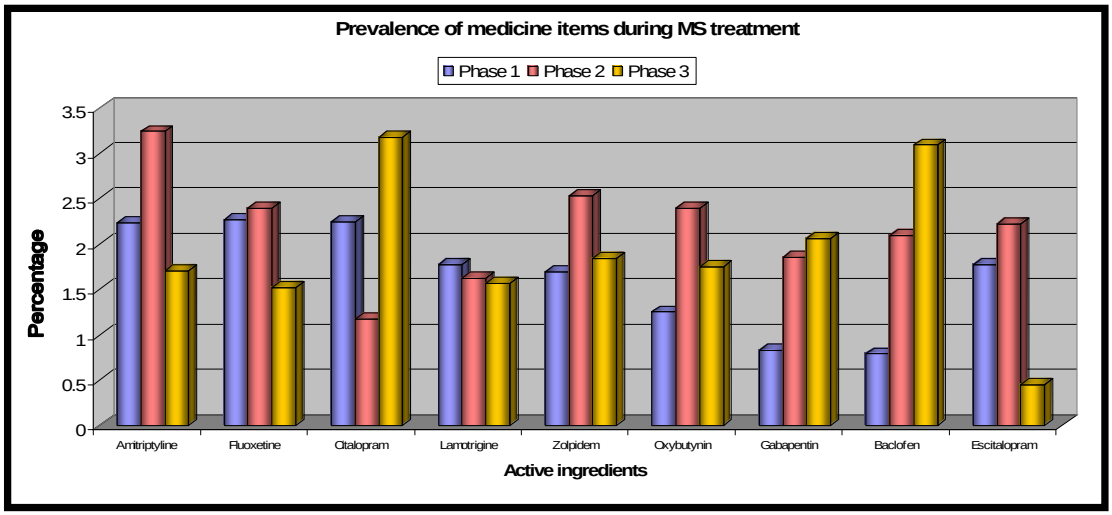

Figure 4.26 Percentages of active ingredients indicated for MS during each phase of the treatment

Figure 4.26 shows that the percentages of all the symptomatic treatments of MS decreased after these patients had been treated with biologic immunomodulators, but while they were receiving treatment with interferons (phase two) the percentages of medicine items to treat the symptoms of MS increased rather significantly. It was especially those items indicated to treat MS related depression and pain and paroxymal symptoms that increased during phase two of treatment. As stated by Serono, Inc., 2003 (refer to Table 2.18), this might be ascribed to the fact that depression and flu-like symptoms are common adverse events associated with the use of beta interferons. The increased frequency of antidepressants and pain medication like baclofen may thus be attributed to side-effects of beta interferons.

After treatment with biologics, however, the percentages of the top ten other medicine items claimed for MS patients decreased from they had been before treatment with biologics. This could be an indication that treatment with beta interferons improved the symptoms of MS in the long run, but treatment outcomes were not measured in this study, which limits the applicability of this conclusion. The decrease in the percentages of the top ten agents could also be because of changes in the composition of prescriptions claimed for MS patients, but because this phenomenon was also not investigated, the applicability of this statement is also limited.

This section showed how the frequencies of specific medicine items changed from phase one of MS treatment to phase three during the four years. The following sections will focus on the frequencies and costs of all the medicine items (and prescriptions) claimed for MS patients between 2005 and 2008, and how these changed from one phase to another.

4.4.2.3 Number of medicine items and prescriptions claimed for MS patients

Section 4.4.2.1 showed that the top ten medicine items (among which were certain specific medicine items used to treat the symptoms associated with MS) decreased considerably after patients with this disease had been treated with biological medicine items. Table 4.6.5 (compiled from Tables A.28.1.1 to A.29.4.2 in appendix B) summarises the total number of medicine items and prescriptions claimed for MS patients during each phase of their treatment between 2005 and 2008.

According to Table 4.6.5, the number of other medicine items and prescriptions claimed for MS patients decreased from before to after treatment with biologic immunomodulators. Before treatment with interferons, 6,171 medicine items and 3,008 prescriptions, were claimed for MS patients, but after treatment with interferons, the number of medicine items (n = 2,234) medicine items and prescriptions (n = 976) decreased with 176.23% and 208.20% respectively.

Table 4.6.5 Number of medicine items and prescriptions claimed for MS patients

Number of items												
Phase		*Gender*		*Age group*				*Prescriber*				
	Total	*M*	*F*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	**6,171**	864	5,307	339	1,267	4,416	149	3,634	994	1,187	310	46
Phase 2	**14,321**	2,525	11,796	708	2,463	10,504	646	5,001	6,787	1,920	563	50
Biologics	4,106	841	3,292	201	1,057	2,736	112	200	3,887	14	5	0
Other	10,215	1,711	8,054	507	1,406	7,768	534	4,801	2,900	1,906	558	50
Phase 3	**2,234**	146	2,088	71	249	1,515	399	1,249	599	308	77	1
Number of prescriptions												
Phase		*Gender*		*Age group*				*Prescriber*				
	Total	*M*	*F*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	**3,008**	398	2,610	164	690	2,077	77	1,643	505	696	127	37
Phase 2	**8,986**	1,638	7,348	445	1,710	6,507	316	2,417	5,238	1,049	249	33
Biologics	4,053	795	3,528	199	1,035	2,707	112	198	3,836	14	5	0
Other	4,933	843	4,090	246	675	3,800	204	2,219	1,402	1,035	244	33
Phase 3	**976**	95	881	48	150	674	104	493	276	173	33	1

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Prescriber: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

However, during the period while MS patients were receiving treatment with biologics (phase two), the total number of medicine items and prescriptions increased significantly from before treatment with biologics. More than double the number of medicine items (n = 14,321) and prescriptions (n = 8,986) were claimed during phase two of MS treatment, unlike any other phase. Furthermore, based on Table 4.6.5, of all the medicine items claimed during phase two, 28.67% were biologic immunomodulators and the rest were other medicine items, whereas 45.10% of all the prescriptions claimed during this phase contained biological medicine items.

According to Table 4.6.5, the largest percentage of medicine items and prescriptions claimed during each phase of MS treatment were for female patients. More than 80% of the other medication claimed for MS patients between 2005 and 2008 were for female patients and 80% of the biological medicine items and 87% of the biologic prescriptions were claimed for female MS patients. This can be attributed to the fact that more than eighty per cent of all the patients on the database who were identified as MS patients between 2005 and 2008, were female (refer to section 4.4.2.1).

During each phase of MS treatment, the largest percentage of the medicine items and prescriptions were claimed for MS patients between the ages of 40 and 64 years (age group three). Before treatment with biologics, approximately 70% of the medicine items (n = 4,416) and prescriptions (n = 2,077) were claimed for MS patient between the ages of 40 and 64 years (age group four). Patients between 25 and 39 years (age group two) received approximately 21% of the medicine items (n = 1,267) and prescriptions (n = 690) during this phase, whereas the number of medicine items (n = 149) and prescriptions (n = 77) claimed for patients older than 64 years (age group four), represented the smallest percentage (2.4%) of all the medicine items and prescriptions claimed before treatment with biologics.

During and after treatment with biologic immunomodulators, the ratio of medicine items and prescriptions claimed for the patients in each age group remained unchanged, as patients between 40 and 64 years still received the largest percentage of all the medicine items and prescriptions, followed by patients younger than 40 years (age groups one and two), while the smallest number of medicine items and prescriptions had been claimed for MS patients older than 64 years. This indicates that it was mainly MS patients between the ages of 25 and 64 years who claimed the most medication during each phase of their treatment. It was also these patients who received the largest number of biologic immunomodulators during phase two of MS treatment (refer to Table 4.6.5). This was, however, not unexpected, since more than sixty per cent of all the MS patients on the database who received biologics between 2005 and 2008 were between the ages of 40 and 64 years; approximately thirty per

cent were between the ages of 25 and 39 years; seven per cent were younger than 25 years and those below three per cent were older than 64 years (refer to section 4.4.2.1).

Before MS patients started receiving biological medicine, most of their medication was prescribed by general practitioners and other prescribers (group three). More than 50% of the medicine items and prescriptions claimed for MS patients during phase one were prescribed by general practitioners, and about 20% were prescribed by "other" prescribers. During this phase of treatment, medicine items and prescriptions prescribed by neurologists only represented about 17% of the total number of medicine items and prescriptions claimed (refer to Table 4.6.5).

However, during phase two of MS treatment, 47.39% of the medicine items and 58.29% of all the prescriptions were prescribed by neurologists. The largest percentage (approximately 45%) of other medicine items and prescriptions were still prescribed by general practitioners, whereas 28% and 19% were prescribed by neurologists and "other" prescribers respectively. On the other hand, 94% of all the biologics (i.e. beta interferons) were prescribed by neurologists, whereas less than 5% were prescribed by general practitioners and less than 1% was prescribed by "other" prescribers (refer to Table 4.6.5).

After treatment with biologics had stopped, most of the medicine items and prescriptions (about 55%) were once again prescribed by general practitioners, followed by about 24% prescribed by neurologists and 14% prescribed by "other" prescribers. The smallest number of medicine items and prescriptions during all three phase of MS treatment were prescribed by specialists in groups four (below 5%) and five (below 1%) (i.e. rheumatologists, oncologists etc.) (refer to Table 4.6.5). Thus, before, during and after treatment with biologic immunomodulators, most of the prescriptions that did not contain biological medicine items that were claimed for MS patients were prescribed by general practitioners, followed by "other" prescribers and neurologists, but while they were being treated with biologics, most of the prescriptions for interferons were prescribed by neurologists (refer to Table 4.6.5). This is in line with the prescribing guidelines of biologics indicated for MS (i.e. beta interferons), as neurologists are supposed to evaluate patients before they start treatment with these agents (Multiple sclerosis South Africa, 2010) (refer to section 3.4.1.3).

From Table 4.6.5 it is thus clear that the total number of medicine items and prescriptions claimed for MS patients after they had been treated with interferons was significantly lower than before they received treatment with these biologics. Table 4.6.6 in section 4.4.2.4 indicates how the average number of medicine items per prescription per MS patient was influenced by the use if interferons during the second phase of their treatment.

4.4.2.4 Average number of medicine items per prescription per MS patient

Table 4.6.6 indicates how the average number of medicine items per prescription for a patient with MS was affected by beta interferons (or biologic immunomodulators) during phase two of their treatment. According to Table 4.6.6, the average number of medicine items per prescription per patient during the first phase of MS treatment was seldom more than two (1.92 ± 0.83) regardless of their gender or age.

During (2.03 ± 0.98) and after (2.06 ± 1.29) treatment with biologics, the average number of other medicine items (excluding biologics) per prescription per patient increased, but not significantly (*d*-value = 0.02). This increase in the average number of medicine items per prescription may be ascribed to changes in the composition of the prescriptions, or the arrival of new medicine items or trade names to the market.

Table 4.6.6 Average number of medicine items per prescription per MS patient

Phase		***Average number of items/Rx***	***Average number of items/Rx: Gender***		***Average number of items/Rx: Age***			
			Male	*Female*	*Age group 1*	*Age group 2*	*Age group 3*	*Age group 4*
Phase 1		1.92 ± 0.83	1.91 ± 1.03	1.93 ± 0.79	1.76 ± 0.54	1.91 ± 0.53	1.96 ± 0.96	1.58 ± 0.62
Phase 2	***Biologics***	2.48 ± 5.02	2.92 ± 8.97	2.39 ± 3.80	2.82 ± 5.44	2.20 ± 3.86	2.56 ± 5.57	2.93 ± 2.68
	Other	2.03 ± 0.98	1.90 ± 0.80	2.05 ± 1.01	1.66 ± 0.57	1.98 ± 0.73	2.02 ± 0.99	2.46 ± 2.39
Phase 3		2.06 ± 1.29	1.48 ± 1.03	2.18 ± 1.31	1.41 ± 0.55	1.88 ± 1.25	2.15 ± 1.31	2.50 ± 1.78

The average number of biological medicine items per prescription per patient (2.48 ± 5.02) was also higher than the average number of other medicine items per prescription for both male and female patients of all ages. Male MS patients received more biologic immunomodulators per prescription (2.92 ± 8.97) than female MS patients (2.39 ± 3.80), but the difference was not practically significant (*d*-value = 0.06) (refer to Table 4.6.6).

The average number of biologics per prescription did not differ much between MS patients of different ages, but the number of other medicine items (other than biologics) per prescription also claimed during the second phase of MS treatment was slightly higher for patients between 40 and 64 years (2.02 ± 0.99) and patients older than 64 years (2.46 ± 2.39) than for patients between 25 and 39 years (1.98 ± 0.73) and patients younger than 25 years (1.66 ± 0.57) (refer to Table 4.6.6).

On average, there was a slight increase in the average number of medicine items per prescription per patient from before (1.92 ± 0.83) to after (2.06 ± 1.29) treatment with biologic immunomodulators, but when analysed according to gender and age groups, it can be seen that the average number of medicine items per prescription per MS patient decreased for male patients from before (1.91 ± 1.03) to after (1.48 ± 1.03) treatment with biologics, whereas the average number of medicine items per prescription increased for female MS patients from before (1.93 ± 0.79) to after (2.18 ± 1.31) treatment with these agents. The average number of other medicine items per prescription also decreased for patients younger than 40 years from before to after treatment with biologic immunomodulators, whereas it increased slightly for MS patients older than 39 years (refer to Table 4.6.6). However, the differences in the average number of medicine items per prescription between MS patients of different ages were not practically significant (*d*-values below 0.2). The average number of medicine items per prescription according to prescriber is summarised in Table A.30 in appendix B. Since these values are not *per patient*, they will not be discussed in this section.

Thus, the total number of medicine items and prescriptions claimed for MS patients between 2005 and 2008 decreased after they received treatment with biologic immunomodulators, whereas the average number of medicine items per prescription increased slightly. Section 4.4.2.5 investigates how the average costs of these medicine items and prescriptions changed over the three phases of MS treatment during the four-year period.

4.4.2.5 Average cost per medicine item and prescription for MS patients per phase

This section discusses the data in Tables A.28.1.1 to A.29.4.2 in appendix B. According to Tables A.28.11 and A.29.1.1, the average cost per medicine item and the average cost per prescription claimed for MS patients before treatment with biologics had started, were R133.24 ± 146.80 (mean = R79.66) and R273.34 ± 320.81 (mean = R179.08) respectively.

When MS patients started treatment with beta interferons, however, the average cost per medicine item (R2268.35 ± 3387.05) (median = R166.84) and prescription (R3615.07 ± 3733.46) (median = R813.31) increased with 1602.45% and 1222.55% respectively. The median values, however, show that the cost of most medicine items and prescriptions increased with 109.44% and 354.16% respectively. The reason for the significant increase in the average costs is because high cost biological medicine items (i.e. beta interferons) were also claimed during this phase of MS treatment, and even though they are only a few, their considerable costs influences the average medication cost drastically. The separation of the

cost of biologics and "non-biologics" or other medicine items (as shown in Table A.28.1.2) illustrates this point: the average cost of a prescription that contained a biologic immunomodulator (R7629.00 ± 1169.91) was significantly higher than the average cost of a prescription that did not contain these medicine items (R316.74 ± 379.31) (median = R185.67) (*d*-value = 6.25). The average cost of biologics was thus approximately 2300% higher than the average cost of other medicine items (refer to Table A.28.2 in appendix B).

After treatment with biologics had stopped, the average cost per medicine item (R170.01 ± 206.92) (median = R112.51) and prescription (R389.14 ± 498.34) (median = R224.92) were 1234.25% and 828.99% lower than during phase two, but 27.60% and 42.36% higher than during phase one. The average cost of other medicine items (excluding biologics) thus increased from before to after treatment with biologics (refer to Table A.28.1.1 and A.28.1.2 in appendix B). The increase in the average cost per medicine item and the average cost per prescription was in reality inevitable, since medical inflation and the increase in the price of consumer products (which also includes medicine) caused price increases.

- *Average cost per medicine item and prescription for MS patients according to gender*

During the first phase of MS treatment, the average cost per medicine item was 7.53% lower for a female (R131.85 ± 147.35) (median = R78.71) than for a male patient (R141.78 ± 143.15) (median = R101.12) and the average cost per prescription for a female patient (R268.09 ± 300.07) (median = R185.60) was 14.80% lower than for a male (R307.78 ± 431.76) (median = R162.61). The median values, however, show that the cost of most prescriptions claimed for female patients (median = R185.60) was higher than the cost of most prescriptions claimed for male MS patients ((median = R162.61). The higher average cost of prescriptions for male patients might be because one or two patients received high priced medicine items during this phase or because more than one month's treatment was claimed for a patient on one occasion.

During phase two of MS treatment, the average cost per other medicine item and the average cost of biologic immunomodulators were higher for female patients than for male patients, but the average cost of both biologics and other prescriptions was higher for males. The average cost of a biologic prescription (R7663.40 ± 1293.55) was 0.55% higher for male MS patients than for female MS patients (R7621.28 ± 1137.76), whereas the average cost of other prescriptions was 19.04% higher for males (R365.17 ± 295.43) (median = R237.59) than for females (R306.75 ± 375.17) (median = R180.06) (refer to Tables A.28.2.1 and A.28.2.2).

After treatment with biologics, the average cost per medicine item for a female MS patient (R168.40 ± 205.22) (median = R108.82) was 14.64% lower than for a male (R193.06 ± 229.39) (median = R127.45), but the average cost per prescription was 34.52% higher for a female patient (R399.11 ± 511.31) (median = R225.83) than for a male patient (R296.70 ± 344.73) (median = R179.15).

Thus, before treatment with biologic immunomodulators, the average cost per medicine item was higher for females with MS, but after treatment with biologics it was higher for males, whereas the average cost per prescription was higher for male MS patients during the first phase of MS treatment, but higher for females during the last phase (refer to Table A.28.2.1). The difference in the average medicine item costs and the average prescription costs between males and females could be put down to the difference in the type of medicine items used by males and females, and also differences in the composition of males' and females' prescriptions.

- *Average cost per medicine item and prescription for MS patients according to age groups*

The average cost of medication was basically the same for the patients in all age groups. Table 4.6.7 (compiled from Tables A.28.3.1 and A.28.3.2 in appendix B) summarises the average cost of medicine items and prescriptions for MS patients according to age.

Table 4.6.7 indicates that the average cost of other medicine items and prescriptions claimed for MS patients during phase one was the highest for patients older than 64 years (age group four), and the lowest for patients younger than 25 years (age group one), whereas the average costs of medicine items and prescriptions claimed by patients between 25 and 39 years (age group two) and patients between 40 and 64 years (age group three) were relatively the same.

Table 4.6.7 furthermore shows that during phase two of MS treatment, the average cost per biological medicine item and the average cost per biologic prescription were relatively the same, and the average cost per biologic prescription for patients in all four age groups also differed very much (R7883.05 ± 868.81 for group one; R7595.93 ± 1232.51 for group two; R7623.66 ± 1170.72 for group three and R7631.89 ± 962.58 for group four).

Table 4.6.7 Average cost per medicine item and prescription for MS patients according to age groups

Average cost per medicine item				
Phase	Age group 1	Age group 2	Age group 3	Age group 4
Phase 1	93.98 ± 98.43	131.83 ± 159.86	135.95 ± 146.00	154.10 ± 132.38
Phase 2	2318.43 ± 3481.38	3272.41 ± 3680.44	2081.02 ± 3290.74	1431.15 ± 2871.87
Biologics	7804.62 ± 748.11	7437.83 ± 1051.86	7542.85 ± 1064.16	7631.89 ± 962.58
Other	143.43 ± 131.32	140.94 ± 195.86	157.29 ± 187.36	130.62 ± 117.79
Phase 3	150.36 ± 93.22	121.73 ± 139.66	186.52 ± 235.09	140.94 ± 113.48
Average cost per prescription				
Phase	Age group 1	Age group 2	Age group 3	Age group 4
Phase 1	194.26 ± 173.89	242.08 ± 255.65	289.05 ± 348.37	298.19 ± 264.46
Phase 2	3688.64 ± 3826.17	4713.42 ± 3703.69	3359.31 ± 3689.89	2925.71 ± 3551.55
Biologics	7883.05 ± 868.81	7595.93 ± 1232.51	7623.66 ± 1170.72	7631.89 ± 962.58
Other	295.61 ± 266.21	293.58 ± 358.10	320.94 ± 389.49	340.26 ± 368.96
Phase 3	222.41 ± 163.24	202.07 ± 245.67	419.26 ± 547.88	540.70 ± 443.86

After treatment with biologics had stopped, however, the average cost per medicine item as well as the average cost per prescription was significantly higher for patients older than 39 years (age groups three and four) than for patients younger than 40 years (age groups one and two) (*d*-values ~ 0.7). The average cost per prescription claimed for MS patients older than 64 years was 167.58% higher than the average cost per prescription claimed for patients between the ages of 25 and 39 years, and 143.11% higher than the average cost per prescription claimed for patients younger than 25 years. The average cost per prescription claimed for patients between 40 and 64 years was 88.51% and 107.48% higher than the average cost per prescription claimed for patients in age groups one and two respectively.

Before and during treatment with biologic immunomodulators, the average cost of other medicine items and prescriptions (excluding biologics) did not differ much between MS patients of different ages. The average cost per biologic immunomodulator was also relatively the same for all MS patients, bur after treatment with biologics had stopped, the average cost of medicine items and prescriptions was higher for older MS patients (all MS patients older than 39 years) than for the younger patients. Furthermore, the average cost per prescription increased from phase one to phase three for patients in age group one (with about 14%), age group three (with about 45%) and age group four (with about 81%), but decreased for patients in age group two (with 19.80%). The largest increase in the average prescription cost was thus also for patients older than 39 years (refer to Table 4.6.6).

The average cost per medicine item also increased from before to after treatment with biologics for age groups one (59.99%) and three (37.20%), but decreased for age groups two and four, with 8.30% and 9.34% respectively. The difference in the average medicine item and prescription cost between the different age groups during phases one and two, was not practically significant (*d*-values below 0.2), but the effect of the difference in the average prescription cost between MS patients older than 64 years and those younger than 40 years (age groups one and two) during phase three, was large and practically significant (*d*-value larger than 0.7) (refer to Table 4.6.6). This could be ascribed to the fact that patients older than 64 years are more prone to chronic diseases such as cholesterol, blood pressure, heart diseases etc., that more often than not require relatively expensive chronic medication.

- *Average cost per medicine item and prescription for MS patients according to prescriber*

When the average cost per prescription is compared between different prescribers, the following could be determined: during phase one of MS treatment, the prescriptions prescribed for MS patients by specialists (prescriber group four), had a higher average cost (R380.67 ± 369.70) when compared to the average cost per prescription prescribed by a neurologist (348.26 ± 309.03), but the average cost per medicine item prescribed by a neurologist was the highest (R176.93 ± 183.70). The average cost per prescription prescribed by a general practitioner (R255.11 ± 324.66) and other prescribers (R248.34 ± 305.04) was lower than that of prescriptions prescribed by neurologists and group four specialists, but higher than the average cost per prescription prescribed by a specialist in group five (R162.57 ± 134.29) (refer to Table A.28.4.1). When the median values are taken into account, it is seen that the cost of most of the prescriptions prescribed by general practitioners (median = R165.07) was higher than the cost of most prescriptions prescribed by group five prescribers (median = R150.05) and group three prescribers (median = R144.49) and that the cost of most prescriptions prescribed by neurologists was lower than the costs of any other prescriptions (median = R103.46).

During phase two of MS treatment, the average cost per biologic immunomodulator was very nearly the same when prescribed by all prescriber types (approximately seven thousand six-hundred rand). The average cost per biologic immunomodulator was only slightly higher (R7928.62 ± 100.02) when prescribed by “other” prescribers (group three) (refer to Table A.28.4.2).

After treatment with biologic immunomodulators, however, the average cost per prescription prescribed by a specialist in group four (R314.10 ± 336.17) (median = R216.37), was lower

than the average cost per prescription prescribed by a neurologist (R517.04 ± 704.88) (median = R251.91). Furthermore, the average cost per prescription prescribed by a neurologist increased with 48.46% between phase one and phase three, whereas the average cost per prescription prescribed by a group four specialist decreased with 21.19%. During phase three of MS treatment, prescriptions prescribed by general practitioners had a higher average cost (R369.94 ± 391.96) (median = R246.91) than prescriptions prescribed by group four specialists and group three prescribers (R256.37 ± 325.43) (median = R152.69). The average cost per prescription prescribed by a general practitioner increased with 45.01% from phase one to three, whereas the average cost per prescription prescribed by prescribers in group three increased with 3.23% (refer to Table A.28.4.1).

The difference in the average cost of prescriptions prescribed before and after treatment with biologics between the different prescriber types was practically insignificant (*d*-values less than 0.2), except for the difference in the average prescription cost between prescriptions prescribed by specialists in group four and group five during phase one (*d*-value = 0.59) (refer to Table A.28.4.1). The average cost per medicine items according to prescribers showed the same basic trend as the prescriptions and will not be discussed in detail (refer to Table A.28.4.1).

When the *d*-value is calculated between the average cost per prescription claimed for an MS patient in phase two (R3615.07 ± 3733.46) (median = R813.31) and the average cost per medicine item claimed in phases one and three, a value of 0.89 is obtained. This indicates that the effect size of prescriptions claimed during phase two of MS treatment is large and practically significant. When the *d*-value between the average cost per biologic prescription (R7629.00 ± 1169.91) (median = R7688.49) and other prescriptions (R316.74 ± 379.31) (median = R185.67) claimed for MS patients during phase two is calculated, a value of 6.25 is obtained, which indicates that the impact of prescriptions that contained biologic immunomodulators was very large and practically significant (refer to Tables A.28.4.1 and A.28.4.2).

This discussion showed that the average cost of biologic immunomodulators used in the treatment of MS was relatively expensive. Table 4.6.8 indicates how many of these prescriptions were claimed for MS patients over the four-year study period to determine how much the average cost of these therapies can amount to.

Table 4.6.8 Average number of biologic prescriptions per MS patient within the four-year study period

Average number of Rx per patient	***Average number of Rx/patient: Gender***		***Average number of Rx/patient: Age***			
	Male	*Female*	*Age group 1*	*Age group 2*	*Age group 3*	*Age group 4*
23.56 ± 14.82	27.41 ± 17.04	22.78 ± 14.27	18.09 ± 9.51	20.70 ± 14.26	25.54 ± 15.26	22.40 ± 16.33

Table 4.6.8 shows that between 2005 and 2008, MS patients received 23.56 ± 14.82 prescriptions per patient within the four-year period. Male MS patients received more biologic prescriptions (27.41 ± 17.04) within the four years than female MS patients (22.78 ± 14.27), but this difference was not practically significant (*d*-value = 0.27). MS patients who were between 40 and 64 years between 2005 and 2008 received the most biologic prescriptions during the study period (25.54 ± 15.26), followed by patients older than 64 years (22.40 ± 16.33) and patients between the ages of 25 and 39 (20.70 ± 14.26). MS patients who were younger than 25 years received the smallest number of biologics prescription during the four-year period (18.09 ± 9.51), but the difference in the average number of prescriptions per MS patient per year between patients of different age groups was not practically significant (*d*-values below 0.2) (refer to Table 4.6.8).

Patients with MS thus received more biologic prescriptions during the four-year period. Even though the average prescription cost for biologic immunomodulators was slightly less for MS patients than for RA patients, the annual cost of these therapies can still amount to extraordinary sums of money each year when an MS patient needs 30µg interferon once a week indefinitely (refer to section 2.7.3.6, page 87) and an average of 24 biologic prescriptions would be claimed per MS patient during four years. Table 4.6.9 in section 4.4.2.6 shows what the total medicine treatment cost for MS patients had been during each phase of their treatment between 2005 and 2008.

4.4.2.6 Analysis of the total medicine treatment cost of MS per phase

Table 4.6.9 was compiled from Tables A.28.1.1 to A.29.4.2 in appendix B and summarises the total medicine treatment cost of MS during each phase.

According to this table, biologic immunomodulators (or interferons) claimed for MS patients between 2005 and 2008, represented 0.41% (R30, 922,520.07) of the total cost (R7, 483,759,176.23) of all the medicine items claimed through the PBM during this period.

Table 4.6.9 Total medicine treatment cost of MS per phase

	Total medicine treatment cost												
Phase	**Variables**		***Gender***		***Age group***				***Prescriber***				
		Total	*Males*	*Females*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*5*
Phase 1	Total	**822,220.75**	122,495.96	699,724.79	31,858.52	167,034.67	600,367.12	22,960.44	419,142.95	175,872.45	172,844.83	48,345.57	6,014.95
	Scheme	670,976.25	110,442.82	560,533.43	25,512.59	142,002.10	481,565.99	21,895.57	346,852.16	149,833.40	125,252.13	44,262.30	4,776.26
	Patient	151,244.50	12,053.14	139,191.36	6,345.93	25,032.57	118,801.13	1,064.87	72,290.79	26,039.05	47,592.70	4,083.27	1,238.69
Phase 2	Total	**32,484,977.66**	6,400,243.71	26,084,733.95	1,641,446.82	8,059,947.00	21,859,058.66	924,525.08	2,112,056.39	29,803,991.08	432,773.85	132,367.05	3,789.29
	Scheme	31,392,633.45	6,204,055.30	25,188,578.15	1,612,390.69	7,770,400.82	21,104,041.70	905,800.24	1,962,700.65	28,963,213.90	349,809.23	113,699.17	3,210.50
	Patient	1,092,344.21	196,188.41	896,155.80	29,056.13	289,546.18	755,016.96	18,724.84	149,355.74	840,777.18	82,964.62	18,667.88	578.79
Biologics	Total	**30,922,520.07**	6,092,405.10	24,830,114.97	1,568,727.66	7,861,783.45	20,637,237.15	854,771.81	1,528,106.63	29,245,671.07	111,000.62	37,741.75	0.00
	Scheme	30,183,184.60	5,955,081.72	24,228,102.88	1,562,849.46	7,621,467.25	20,155,717.53	843,150.36	1,521,344.43	28,513,097.80	111,000.62	37,741.75	0.00
	Patient	739,335.47	137,323.38	602,012.09	5,878.20	240,316.20	481,519.62	11,621.45	6,762.20	732,573.27	0.00	0.00	0.00
Other	Total	**1,562,457.59**	307,838.61	1,254,618.98	72,719.16	198,163.65	1,221,821.51	69,753.27	583,949.76	558,320.01	321,773.23	94,625.30	3,789.29
	Scheme	1,209,448.85	248,973.58	960,475.27	49,541.23	148,933.57	948,324.17	62,649.88	441,356.22	450,116.10	238,808.61	75,957.42	3,210.50
	Patient	353,008.74	58,865.03	294,143.71	23,177.93	49,230.08	273,497.34	7,103.39	142,593.54	108,203.91	82,964.62	18,667.88	578.79
Phase 3	Total	**379,800.98**	28,186.67	351,614.31	10,675.68	30,310.23	282,581.81	56,233.26	182,379.80	142,703.13	44,352.83	10,365.22	0.00
	Scheme	303,015.24	20,433.29	282,581.95	8,458.39	22,470.05	230,695.76	41,391.04	137,983.42	124,144.41	33,097.36	7,790.05	0.00
	Patient	76,785.74	7,753.38	69,032.36	2,217.29	7,840.18	51,886.05	14,842.22	44,396.38	18,558.72	11,255.47	2,575.17	0.00

Based on Table 4.6.9, interferon beta-1a and interferon beta-1b represented 91.79% of the total treatment cost of MS (R33, 686,999.39) for the four-year period. Other medicine items (excluding biologics) claimed before treatment with interferons represented 2.44% (R822, 220.75) of the total medicine treatment cost of MS, whereas the medication claimed after treatment with interferons represented only 1.13% (R379, 800.98).

From Table 4.9.6 it is clear that the cost of MS treatment was significantly higher during phase two, during which MS patients received interferons. Interferons represented 95.19% of the total medicine cost of phase two (R32, 484,977.66), whereas other medication (excluding biologics) represented 4.81% (R1, 562,457.59). From Tables A.28.1.2 and A.29.1.2, the percentage frequency of biologic immunomodulators can be determined. According to these tables, biologics only represented 28.67% of all the medicine items and 45.10% of all the prescriptions claimed during phase two of MS treatment, but they represented 95.19% of the total medicine cost of this phase. When the CPI of interferons used in the treatment of MS is calculated and the cost percentage (95.19%) is divided by the frequency percentage of the medicine items (28.67%), a value of 3.3 is determined, whereas when the cost percentage is divided by the frequency percentage of the prescriptions (45.10%), a value of 2.11 is obtained. Both these values are significantly higher than one, which indicates that interferons used to treat MS are relatively expensive.

However, after treatment with interferons had stopped, the total cost of other medication (excluding biologics) (R379, 800.98) decreased with 116.49% from before treatment with biologics, which indicates that despite that high cost of interferons, the total treatment cost with other medication decreased after treatment with these biologic immunomodulators (refer to Table 4.6.9). This can be ascribed to the fact that the total number of medicine items and prescriptions claimed for MS patients also decreased from before to after treatment with biologics (refer to Table 4.6.5 and section 4.4.2.3).

When the total medicine treatment cost of MS is compared between male and female MS patients and MS patients of different ages, it is clear that the total cost of treatment decreased from before to after treatment with biologics for all the MS patients on the PBM database between 2005 and 2008, regardless of their gender or age, but it is shown that 85% of the total medicine cost during phase one as well as 93% of the total medicine cost during phase three was represented by medication claimed for female MS patients and 80% of the cost of interferons was also represented by biologics claimed by females (refer to Table 4.6.9). Thus, the larger percentage of the total medicine treatment cost of each phase of MS treatment was represented by female patients, which was expected since female MS

patients received far more medicine items and prescriptions than male MS patients (refer to Table 4.6.5).

Furthermore, more than 70% of the total cost of medicine claimed during phase one and three was represented by medication claimed by patients between 40 and 64 years (age group three). Before treatment with biologics, medication claimed for patients between 25 and 39 years (age group two) represented 20.32% of the total medicine cost, whereas those claimed for patients younger than 25 years (age group one) and older than 64 years (age group four) represented only about 3% each. The same is true for the cost of biologics: biologics claimed for patients between the ages of 40 and 64 years represented 66.74% of the total cost of biologics, and medication claimed by patients between the ages of 25 and 39 represented 25.42%, whereas the remaining 8% was represented by patients younger than 25 years and those older than 64 years (refer to Table 4.7.9). This is also in line with the number of medicine items and prescriptions claimed for each age group between 2005 and 2008: most of the medication claimed for MS patients was for patients between 40 and 64 years, and the lowest was for patients older than 64 years (refer to Table 4.6.5).

After treatment with biologics, however, medication claimed for patients older than 64 years represented the second largest percentage (14.81%) of the total treatment cost of phase three, following after the cost of medication claimed for patients between 40 and 64 years (74.40%). This can again be ascribed to the distribution of the number of medicine items and prescriptions according to age groups: during phase three of MS treatment, patients older than 64 years received more medicine items than patients between 25 and 39 years (refer to Table 4.6.5).

Table 4.6.9 shows that before treatment with biologic immunomodulators, the largest percentage of the medicine expenditure on MS patients went towards prescriptions prescribed by general practitioners (50.98%), followed by prescriptions prescribed by neurologists (21.39%) and other prescribers (group three) (21.02%). Less than 7% of the total medicine cost of phase one went towards medication prescribed by specialists in groups four (5.88%) and five (0.73%). On the other hand, during treatment with biologics, 94.58% of the total cost of biologics went towards prescriptions prescribed by neurologists, and only 4.94% went towards prescriptions prescribed by general practitioners. No interferons were prescribed by prescribers in group five during phase two of MS treatment.

Based on Table 4.6.9, after treatment with biologics, 48.02% of the total medicine expenditure on MS went towards medication prescribed by general practitioners, and 37.57% went towards medication prescribed by neurologists. The remaining 14% went towards

medication prescribed by those prescribers in groups three, four and five. Thus, before and after treatment with interferons, almost half of the medicine expenditure for MS patients was represented by medication prescribed by general practitioners, and less than one third was represented by medication prescribed by neurologists, but while MS patients were treated with biologic immunomodulators, almost 95% of the total cost of biologics was represented by prescriptions from neurologists, because most of the prescriptions for biologics were from neurologists (refer to Table 4.6.5).

Table 4.6.9 thus indicates that total medicine treatment cost of MS with other medication (excluding biologics) decreased from before to after treatment with interferons. However, the data discussed in sections 4.4.2.5 and 4.4.2.6 were not *per MS patient*, but *per treatment phase*, which did not take into account differences between individual patients. Section 4.4.2.7 will present a discussion on the average cost per medicine item and prescription per MS patient, as well as the total medicine treatment cost per MS patient.

4.4.2.7 Average cost per medicine item per MS patient and the average cost per prescription per MS patient

Table 4.6.10 summarises the average cost per medicine item and the average cost per prescription per patient for those patients identified as MS patients during the study period.

Table 4.6.10 Average cost per medicine item and prescription per MS patient

Average cost per medicine item per patient					
Phase		*Patients*	*Total item cost*	*Medical aid scheme*	*Levy*
Phase 1		132	128.84 ± 82.72	109.21 ± 73.56	19.63 ± 25.54
Phase 2	*Biologics*	172	7536.09 ± 743.56	7359.82 ± 959.32	176.27 ± 510.93
	Other	150	139.80 ± 92.35	108.70 ± 85.47	31.10 ± 40.42
Phase 3		90	144.19 ± 102.57	106.31 ± 88.68	37.88 ± 64.11
Average cost per prescription per patient					
Phase		*Patients*	*Total Rx cost*	*Medical aid scheme*	*Levy*
Phase 1		132	129.47 ± 82.88	109.86 ± 73.77	19.61 ± 25.04
Phase 2	*Biologics*	172	7536.09 ± 743.56	7359.82 ± 959.32	176.27 ± 510.93
	Other	150	141.91 ± 94.78	110.71 ± 88.09	31.20 ± 40.33
Phase 3		90	145.24 ± 102.99	107.09 ± 89.25	38.15 ± 64.10

Based on Table 4.6.10, there were 172 patients with MS on the database who received biologic immunomodulators during the four-year study period, and of these 132 (76.74%) received other medication before starting treatment with biologics (i.e. phase one). During phase two, when the MS patients received biologics, 150 (87.21%) also received other medicine items, which means that 22 (12.79%) MS patients received beta interferons (or biologics) only during that period. The number of MS for whom medication was claimed through the PBM between 2005 and 2008 decreased with 46.67% from before to after treatment with biologics, since only 90 MS patients received medication during phase three of MS treatment.

There could be various explanations for the differences in the number of MS patients in each treatment phase:

- There were 40 MS patients who either defied the treatment protocol of MS and immediately started treatment with biological medicine (i.e. beta interferons), without using the other medication in the treatment algorithm, or who only joined the medical aid scheme when they started treatment with biologics.

- Eighty-two of the MS patients who received biologics did not receive any other medication after their treatment with these agents, or left the medical aid scheme after treatment with the beta interferons had stopped.

Because the researcher did not have direct access to individual patients, the validity of the possible reasons for the differences in the patient numbers was difficult to confirm.

Furthermore, from Table 4.6.10 it is clear that between 2005 and 2008, the average cost per medicine item per MS patient and the average cost per prescription per MS patient for the other medicine items and prescriptions were practically the same (because most prescriptions only contained one medicine item). Therefore, the average cost of medication per patient will only be discussed in terms of the average cost per prescription per MS patient.

Before treatment with interferons, the average cost per prescription per patient was R129.47 ± 82.88. The medical aid scheme paid 84.85% of the total prescription cost during phase one and the patient co-paid the remaining 15.15%, which was not much as the average patient levy was only R19.61 ± 25.04 (median = R10.14). The average cost of other medication (excluding biologics) increased with 9.61% from phase one to phase two, but the average cost of a prescription that contained biological medicine items (R7536.09 ± 743.56) was 5720.72% higher than the average cost of a prescription that did not contain these

medicine items claimed during phase one. This was significantly more than the average cost of other prescriptions (excluding biologics) claimed for MS patients between 2005 and 2008 (*d*-value = 9.9). Furthermore, the medical aid scheme paid 97.66% of the total cost of a biologic prescription. Even though the percentage contributed by an MS patient to the final prescription cost was below 4%, the average patient levy could on occasion be relatively high (R176.27 ± 510.93) (median = R0.00). The contribution of the medical aid scheme to the final prescription cost of non-biologic prescriptions was considerably lower (78.01%), but the burden on the patient was still relatively insubstantial, since the average amount co-paid by an MS patient during phase two of his/her treatment was only R31.20 ± 40.33 (median = R21.29) (refer to Table 4.6.10).

After treatment with interferons, the average cost of other medicine (R145.24 ± 102.99) claimed per MS patient was 12.18% higher than the average cost of medicine items and prescriptions claimed per MS patient before treatment with biologics started. During phase three of MS treatment, the medical aid scheme contributed an even lower percentage (73.73%) of the final prescription cost and the average amount paid by the medical aid scheme also decreased with 2.59% since phase one, whereas the average patient levy increased with 94.54% from before (R19.61 ± 25.04) (median = R10.14) to after (R38.15 ± 64.10) (median = R17.03) treatment with biologics (refer to Table 4.6.10).

The analysis of the average cost per medicine item *per MS patient* and the average cost per prescription *per MS patient* showed the same results as the analysis of the average cost per medicine item and the average cost per prescription *per phase*: the average medicine item costs increased together with increases in average prescription costs, but Table 4.6.9 showed that the total medication cost for MS patients decreased over the four year study period. Thus, the average cost per medicine item and the average cost per prescription claimed for MS patients increased from before to after treatment with biologics, but the total treatment cost of MS decreased from before to after treatment with biologics (refer to Table 4.6.9).

4.4.2.2 Summary of analysis of patients with multiple sclerosis

Between 1 January 2005 and 31 December 2008, there were 172 patients with MS for whom biologic immunomodulators (or beta interferons) had been claimed through the PBM. The ratio of males to females affected by MS was more than 1:4.

According to the literature, the ratio of males to females affected by MS is approximately 2:1 (refer to section 2.7.3.2), which means that the distribution of the MS patients on the database according to gender is in line with the literature. Furthermore, 90.70% of these patients were between the ages of 25 and 64 years (of these two thirds were older than 39 years). This is in accord with the literature which states that it is mostly women and patients in their late twenties and thirties that present with this disease. MS patients furthermore represented 24.12% of all the patients on the PBM database who claimed biologic immunomodulators (n = 713) (refer to Figure 3.1) during this period.

The average cost per medicine item and the average cost per prescription for other medication (excluding biologics) increased from before to after treatment with interferons, together with an increase in the average number of medicine items per prescription. However, the average cost per medicine item and prescription increased for all the medicine items and prescriptions claimed through the PBM between 2005 and 2008, and because the analysis of the treatment of MS also stretched across this same four-year period, an increase in the average medicine cost was not unexpected. It was also almost inevitable, because of the increases in (among others) the prices of consumer products (medicine included) and medical inflation. In opposition, from before to after treatment with interferons, the total number of other medicine items and prescriptions (excluding biologics) claimed by MS patients decreased significantly, which can be ascribed to the fact that the total number of MS patients decreased from phase one to phase three (refer to Table 4.6.10). This also led to a rather sizeable decrease in the total medicine treatment cost of other medicine items between phases one and three of MS treatment.

Therefore, notwithstanding the incredible costs of biologic immunomodulators (interferons) indicated for the treatment of MS and the considerable impact they have on medical aid schemes and patients alike, these medicine items seemed to decrease the number and ultimately the costs of other medicines used in the treatment of MS. However, clinical outcomes were not measured in this study and there is no certain way for the researcher to establish whether the number of medicine items and prescriptions decreased because treatment with interferons improved the disease process, or whether it was because the composition of the prescriptions changed from before to after treatment with biologics.

4.3.3 Analysis of patients with Crohn's disease

The patients discussed in this section includes all the patients who (i) received at least one of the six biologic immunomodulators discussed in this study at least once during the four-year study period, and (ii) had at least two positive diagnostic codes for Crohn's disease (i.e. ICD-10 MPA code: K50, diagnosed code: CD, ICD-10 claim code: CD) at any time between 2005 and 2008.

4.4.3.1 Number of Crohn's disease patients on the database between 2005 and 2008

As for RA and MS, the number of patients with Crohn's disease who received biological medicine between 2005 and 2008 was established prior to investigating the frequencies and costs of their therapies. The total number of patients with Crohn's disease, who received biologic immunomodulators between 2005 and 2008, has been summarised in Table 4.7.1 (compiled from Tables A.36.1 to A.36.3 in appendix B) according to different demographic parameters (i.e. gender, age and prescriber type).

Table 4.7.1 Number of Crohn's disease patients on the database between 2005 and 2008

Total number of patients	Number of patients according to gender		Number of patients according to age group			
11	***Male***	***Female***	***AG 1***	***AG 2***	***AG 3***	***AG 4***
	5	6	3	0	7	1

Table 4.7.1 shows that there were eleven patients with Crohn's disease who received biologic immunomodulators during the four-year period, and of these five were male and six were female. Three of the patients were younger than 25 years (age group one), and one patient was older than 64 years (age group four), but almost two thirds (n = 7) of the patients with Crohn's disease who received biologics between 2005 and 2008, were between the ages of 40 and 64 years (age group three). There were no Crohn's disease patients between the ages of 25 and 39 years (age group two) during the four-year period.

The literature states that Crohn's disease affects mostly adults and that males and females are affected equally (Kappelman *et al*., 2007) (refer to section 2.7.2.2). Since 88% of the Crohn's disease patients were older than 39 years (age groups three and four) and there was only one more male patient than female patient, the distribution of Crohn's disease on the database was relatively in line with the literature.

4.4.3.2 Top ten medicine items and pharmacological groups claimed for Crohn's disease patients during each phase

In this section, the top ten active ingredients and the top ten pharmacological groups will also be compiled for each of the three phases of Crohn's disease treatment between 2005 and 2008. Table 4.7.2.1 and 4.7.2.2 summarises the top ten pharmacological groups and top ten active ingredients claimed for Crohn's disease patients during phase one of their treatment. This includes all the medicine items (excluding biologic immunomodulators) claimed for Crohn's disease patients before starting with biological medicine treatment.

Table 4.7.2.1 Top ten pharmacological groups claimed for Crohn's disease patients during phase 1

Position	Pharmacological code	Description	Frequency	% n
1	12.10.1	Gastro-intestinal tract	80	13.91
2	24.1.1	Immunosuppressants	76	13.21
3	12.4.4	Proton pump inhibitors	45	7.82
4	19.5.1	Corticosteroids	36	6.26
5	7.3.8	ACE inhibitors	24	4.17
6	4.1.3	Specific cyclo-oxygenase-2 inhibitor	21	3.65
7	7.4.2	Beta-receptor blockers	21	3.65
8	7.7.1	Fibrates	21	3.65
9	3.3.1	Analgesics	20	3.47
10	4.1.1	COX-inhibitors	15	2.60
% n = frequency / 575 x 100 **575 = frequency of all the active ingredients claimed during phase 1**				

According to Table 4.7.2.1, the medicine items most frequently claimed for patients with Crohn's disease before they started receiving biologic immunomodulators, were included in pharmacological group 12.10.1 (medicine items indicated for treating disorders of the gastro-

intestinal tract). Based on Table 4.7.2.1, the pharmacological groups also frequently claimed during the first phase of Crohn's disease treatment were immunosuppressants, proton pump inhibitors and corticosteroids.

Table 4.7.2.2 Top ten active ingredients claimed for Crohn's disease patients during phase 1

Position	Pharmacological code	Active ingredient	Description	Frequency	% n
1	24.1.1	Azathioprine	Immunosuppressants	76	13.22
2	12.10.1	Mesalazine	Gastro-intestinal tract	47	8.17
3	12.4.4	Pantoprazole	Proton pump inhibitors	42	7.30
4	19.5.1	Prednisolone	Corticosteroids	31	5.39
5	12.10.1	Sulphasalazine	Gastro-intestinal tract	21	3.65
6	4.1.3	Celecoxib	Specific cyclo-oxygenase-2 inhibitor	21	3.65
7	7.3.8	Perindopril	ACE inhibitors	21	3.65
8	7.4.2	Atenolol	Beta-receptor blockers	21	3.65
9	7.7.1	Bezafibrate	Fibrates	21	3.65
10	23.1.1	Methotrexate	Cytostatics	14	2.43
% n = frequency / 575 x 100 **575 = frequency of all the active ingredients claimed during phase 1**					

When the top ten active ingredients in Table 4.7.2.2 are viewed, the medicine items included in each pharmacological group can be determined. It is clear that the top ten pharmacological groups, as well as the top ten active ingredients prescribed during phase one of Crohn's disease treatment are in line with the treatment protocol of Crohn's disease as stated in the literature (refer to Table 2.15 in chapter 2). According to the literature, the mainstay therapies for treating acute flares of Crohn's disease are the 5-ASA derivates (i.e. sulphasalzine, mesalazine, olsalazine) and corticosteroids (i.e. prednisolone), whereas the treatments of choice to maintain remission of Crohn's disease include immunosuppressive therapies (i.e. azathioprine) as well as methotrexate (McQuaid, 2008:545; Rossiter, 2010:59) (refer to Table 2.15).

Table 4.7.2.2 shows that the active ingredients most frequently claimed during phase one of Crohn's disease were in fact the immunosuppressant azathioprine, and the 5-ASA derivates, mesalzine and sulphasalzine. The other active ingredients also frequently claimed were pantoprazole and the corticosteroid prednisolone. The medicine items most frequently prescribed to Crohn's disease patients in the period before they started treatment with

biologic immunomodulators were in line with the treatment protocol (refer to Figure 2.14 in chapter 2).

According to the literature, the treatment of Crohn's disease usually requires medicine items from more than one pharmacological group, since acute phases of the disease have to be treated in addition to maintaining remission (refer to section 2.7.2.6). Table A.32.1 in appendix B indicates in which combinations therapies for Crohn's disease were most frequently prescribed during phase one of the treatment.

There were not as many combination prescriptions for Crohn's disease patients as for RA and MS. During phase one of Crohn's disease treatment, there were only ten specific combinations of medicine items that were claimed more than once during the four-year period, of which most only contained two medicine items per prescription. Table A.32.1 shows that when medicine items were combined during the first phase of Crohn's disease treatment, the combination usually involved either a 5-ASA derivate (i.e. sulphasalazine, mesalazine, olsalazine) or an immunosuppressant (i.e. azathioprine, methotrexate). Antispasmodics (i.e. mebeverine) and corticosterids (i.e. prednisolone) were also frequently claimed in combination with the 5-ASA derivates and immunosuppressants.

The medicine items which were claimed for Crohn's disease patients during phase two of their treatment are summarised in Tables 4.7.3.1 to 4.7.3.3. Phase two is the period in which Crohn's disease patients received biologic immunomodulators.

Table 4.7.3.1 Biologic immunomodulators claimed for Crohn's disease patients during phase 2

Position	Pharmacological code	Active ingredient	Description	Frequency	% n
1	4.6.1	Etanercept	Musculo-skeletal agent (other)	59	23.05%
2	24.1.1	Adalimumab	Immunosuppressants	48	18.75%
3	12.10.1	Infliximab	Gastro-intestinal tract	21	8.20%
% n = frequency / 256 x 100 **256 = frequency of all the active ingredients claimed during phase 2**					

According to Table 4.7.2.1, 50% of all the medicine items claimed during phase two of Crohn's disease treatment were represented by biologic immunomodulators. The three biologic immunomodulators claimed for Crohn's disease patients are listed in Table 4.7.3.1.

The biologic immunomodulator most frequently claimed for patients with Crohn's disease was etanercept. Etanercept represented 23.05% of all the medicine items claimed during

phase two, and 46.09% of all the biologic immunomodulators claimed for Crohn's disease patients. Adalimumab represented the second largest percentage of all the biologic immunomodulators (37.50%) and 18.75% of all the medicine items claimed for Crohn's disease patients during phase two. Infliximab represented 16.41% of the biologic immunomodulators and 8.20% of all the medicine items claimed for patients with Crohn's disease during this period of their treatment.

Table A.32.2.2 in appendix B shows that the biologic immunomodulators prescribed to Crohn's disease patients were mostly claimed as single therapies. There were, however, three cases where more than one biologic immunomodulator was claimed in combination with each other (i.e. more than one biological medicine item per prescription): there were two occasions on which infliximab appeared twice on one prescription and one occasion on which etanercept appeared twice on one prescription. This might not necessarily be an indication that more than one biologic immunomodulator was used at the same time, but rather that a patient's biologics therapies for a certain period of time had been claimed on the same date. Tables 4.7.3.2 and 4.7.3.3 summarise the top ten pharmacological groups and top ten medicine items also claimed for Crohn's disease patients during phase two of their treatment. These include all the other medicine items (excluding biologic immunomodulators) claimed for Crohn's disease patients during the period they received biological medicine treatment.

Table 4.7.3.2 Top ten pharmacological groups claimed for Crohn's disease patients during phase 2

Position	Pharmacological code	Description	Frequency	% n
1	4.1.1	COX-inhibitors	36	14.06
2	19.3.1	Thyroid agents	35	13.67
3	24.1.1	Immunosuppressants	24	9.37
4	4.7.1	Bisphosphonates	19	7.42
5	19.5.1	Corticosteroids	13	5.07
6	3.3.1	Combination analgesics	12	4.68
7	7.3.8	ACE inhibitors	11	4.29
8	1.3.1	Benzodiazepines	8	3.12
9	12.4.4	Proton pump inhibitors	8	3.12
10	18.1.2	Cephalosporins	8	3.12
11	19.1.2	Oral antidiabetic agents	8	3.12
% n = frequency / 256 x 100 **256 = frequency of all the active ingredients claimed during phase 2**				

Table 4.7.3.3 Top ten active ingredients claimed for Crohn's disease patients during phase 2

Position	Pharmacological code	Active ingredient	Description	Frequency	% n
1	19.3.1	Thyroxine	Thyroid agents	35	13.67
2	24.1.1	Azathiopine	Immunosuppressants	33	12.89
3	4.1.1	Indomethacin	COX-inhibitors	30	11.71
4	4.7.1	Alendronate	Bisphosphonates	19	7.42
5	19.5.1	Prednisolone	Corticosteroids	13	5.07
6	4.1.1	Diclofenac/Misoprostol	COX-inhibitors	8	3.12
7	1.3.1	Diazepam	Benzodiazepines	7	2.73
8	12.10.1	Mesalazine	Gastro-intestinal tract	7	2.73
9	18.1.2	Cefuroxime	Cephalosporins	7	2.73
10	19.1.2	Gliclazide	Oral antidiabetic agents	7	2.73
10	3.3.1	Par/Dextro/Diphen/Caff	Analgesics	7	2.73
10	4.1.1	Diclofenac	COX-inhibitors	7	2.73
10	7.3.8	Lisinopril	ACE inhibitors	7	2.73
10	7.4.1	Diltiazem	Calcium channel blockers	7	2.73

% n = frequency / 256 x 100

256 = frequency of all the active ingredients claimed during phase 2

According to Table 4.7.3.2, the COX-inhibitors and thyroid agents were most frequently claimed in combination with biologic immunomodulators during phase two of Crohn's disease treatment. Together with them, the immunosuppressants, biphosphonates and corticosteroids were also among the top five pharmacological groups claimed during phase two. The frequency of use of the "traditional" immunosuppressants (i.e. azathioprine and mercaptopurine) and 5-ASA inhibitors thus decreased during phase two, and the rest of the top ten pharmacological groups were not the groups indicated for use in Crohn's disease (refer to Table 2.15). Table 4.7.3.3 shows which active ingredients (other than etanercept, adalimumab or infliximab) had the highest frequency during phase two.

The active ingredient most frequently claimed during phase two was thyroxine (indicated for hypothyroidism). The other active ingredient also claimed frequently was azathioprine, which is the immunosuppressant of choice for treating Crohn's disease (Longmore *et al*., 2007:266). Most of the other top medicine items were those not indicated for Crohn's disease, except for prednisolone (position five) and mesalazine (position eight). Table 4.7.3.3 thus indicates that there were not many 'traditional" Crohn's disease medicine items (refer to section 2.7.2.6) claimed as adjunctive therapy during phase two of Crohn's disease

treatment, and that it was mainly the biologic immunomodulators etanercept, adalimumab and infliximab that were claimed during this phase of the treatment.

Furthermore, Table A.32.2.1 in appendix B indicates that the prescriptions that contained more than one medicine item during phase two did not contain medicine items indicated for Crohn's disease. There were only six specific combinations that were claimed more than once during phase three, most of which included thyroxine as one of the medicine items in combination with another medicine item. Based on Table A.32.2.1, Crohn's disease therapies were thus not frequently combined during phase two of the treatment.

All the other medicine items (excluding biologic immunomodulators) and pharmacological groups claimed for Crohn's disease patients after treatment with biological medicine treatment had stopped are summarised in Tables 4.7.4.1 and 4.7.4.2.

Table 4.7.4.1 Top ten pharmacological groups claimed for Crohn's disease patients during phase 3

Position	Pharmacological code	Description	Frequency	% n
1	24.1.1	Immunosuppressants	45	14.95
2	12.10.1	Gastro-intestinal tract	28	9.30
3	3.3.1	Analgesics	24	7.97
4	4.1.3	Specific cyclo-oxygenase-2 inhibitor	18	5.98
5	7.3.8	ACE inhibitors	14	4.65
6	19.5.1	Corticosteroids	10	3.32
7	4.1.1	COX-inhibitors	10	3.32
8	6.1.1	Antihistamines	10	3.32
9	18.7.1	Quinolones	9	2.99
% n = frequency / 301 x 100 **301 = frequency of all the active ingredients claimed during phase 3**				

Table 4.7.4.1 shows that it was again the pharmacological groups specifically indicated for treating Crohn's disease that were prescribed most frequently during phase three of Crohn's disease treatment (refer to Table 2.15 in chapter 2). The immunosuppressants were by far the most frequently claimed pharmacological group during phase three, with the gastro-intestinal tract agents in the second position. The thyroid agents dropped from the first position during phase two, to the last position during phase three. Another pharmacological group used in the treatment of Crohn's disease that was prescribed relatively frequently, was the group containing the corticosteroids (position six) (refer to Table 4.7.4.1).

Table 4.7.4.2 Top ten active ingredients claimed for Crohn's disease patients during phase 3

Position	Pharmacological code	Active ingredient	Description	Frequency	% n
1	24.1.1	Azathiopine	Immunosuppressants	45	14.95
2	4.1.3	Celecoxib	Specific cyclo-oxygenase-2 inhibitor	18	5.98
3	12.10.1	Mesalazine	Gastro-intestinal tract	12	3.99
4	12.10.1	Sulphasalazine	Gastro-intestinal tract	11	3.65
5	19.5.1	Prednisolone	Corticosteroids	10	3.32
6	18.7.1	Ciprofloxacin	Quinolones	9	2.99
7	4.1.1	Indmethacin	COX-inhibitors	9	2.99
8	7.3.8	Perindopril	ACE inhibitors	9	2.99
% n = frequency / 301 x 100 **301 = frequency of all the active ingredients claimed during phase 3**					

Table 4.7.4.2 also indicates the Crohn's disease treatments were most frequently prescribed again during phase three. The immunosuppressant azathioprine, as well as the 5-ASA derivates (mesalazine, sulphasalazine), were the medicine items most frequently claimed during phase three of Crohn's disease treatment. Prednisolone, which is also indicated to treat acute flares of Crohn's disease, was claimed relatively frequently as well (refer to Table 4.7.4.2).

According to Table A.33.3 in appendix B, there were once again prescriptions that combined more than one "traditional" Crohn's disease medicine item during phase three of the treatment. There were only seven specific combinations that were claimed more than once during the four years, but most of them combined the immunosuppressant azathioprine with one or more other traditional treatments (i.e. sulphasalazine, mesalazine, ciprofloxacin).

Figure 4.27 and Figure 4.28 (compiled from Tables 4.7.2.1 to 4.7.4.2) graphically illustrate how the "traditional" Crohn's disease therapies decreased from phase one to phase three of the treatment.

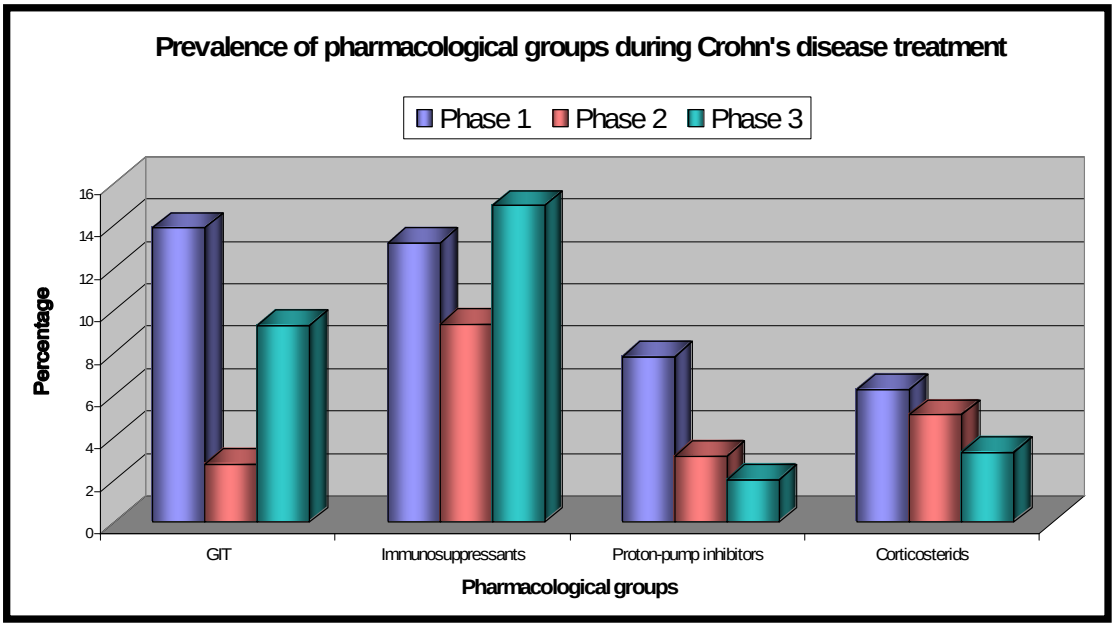

Figure 4.27 Percentages of pharmacological groups indicated for Crohn's disease during each phase of the treatment

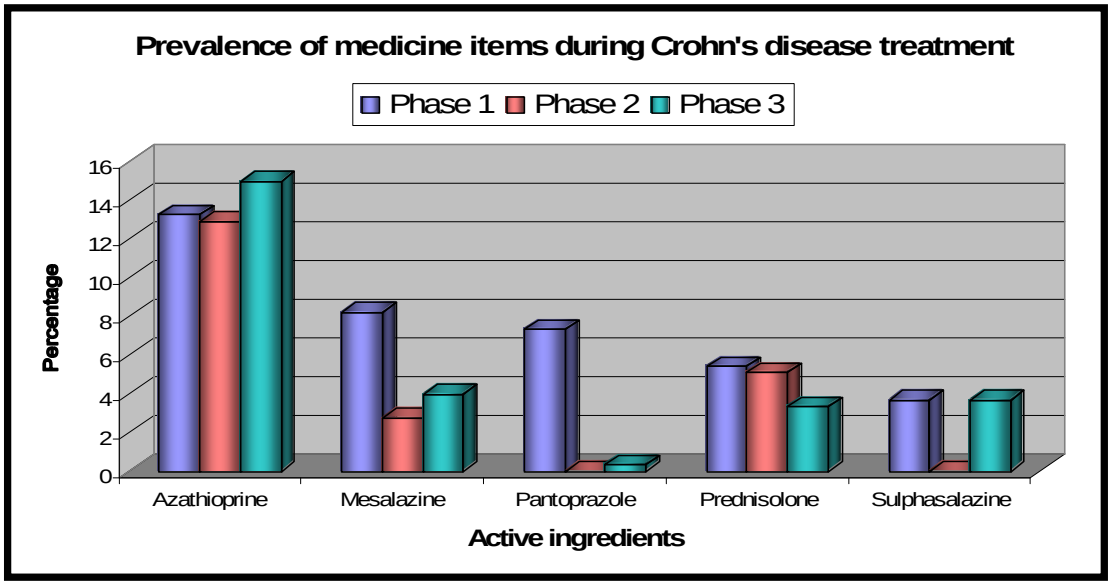

Figure 4.28 Percentages of active ingredients indicated for MS during each phase of the treatment

Figures 4.27 and 4.28 show that the percentages of the medicine items (other than biologics) used to treat Crohn's disease decreased from before to after treatment with biologic immunomodulators. The use of the 5-ASA derivates (i.e. mesalazine and sulphasalazine) and the immunosuppressant azathioprine decreased significantly from phase one to phase two, but increased again after treatment with biologic immunomodulators had stopped. The percentages of these agents during phase three of Crohn's disease treatment were, however, still significantly lower than during phase one. The percentage of corticosteroids

(i.e. prednisolone) and proton-pump inhibitors (i.e. pantoprazole) decreased between each of the three phases (refer to Figure 4.28).

Section 4.4.3.1 follows a discussion on the ways in which the prevalence of the top ten therapies claimed for Crohn's disease patients changed over the course of the three phases of Crohn's disease treatment between 2005 and 2008. According to the analysis, the top ten treatments claimed for these patients decreased from before to after treatment with biologic immunomodulators. This might indicate that after patients with Crohn's disease had been treated with biologic immunomodulators, their condition improved and they did not require as many other medicine items as before, but since clinical outcomes were not measured in this study, the validity of this conclusion is limited. Furthermore, the composition of the prescriptions claimed for these patients before and after treatment with biologics were not investigated, which could also be among the reasons for changes in the frequencies of the medicine items claimed for Crohn's' disease patients.

Sections 4.4.3.3 to 4.4.3.7 will investigate the frequencies of all medication claimed during each phase of Crohn's disease treatment, together with the costs of these therapies and ways in which therapies changed between the different phases of treatment.

4.4.3.3 Number of medicine items and prescriptions claimed for Crohn's disease patients

Section 4.4.3.1 showed that the frequencies of the top ten medicine items claimed for Crohn's disease patients between 2005 and 2008 decreased from phase one to phase three of their treatment. This section investigates the changes in the frequencies and costs of all the medicines claimed for Crohn's disease patients across the course of their treatment between 2005 and 2008.

Table 4.7.5 summarises the number of medicine items and prescriptions claimed for those Crohn's disease patients who received biologics between 2005 and 2008, and divides the distribution according to gender and age groups. Table 4.7.5 was compiled from Tables A.33.1.1 to A.34.4.2 in appendix B.

Table 4.7.5 Number of medicine items and prescriptions claimed for Crohn's disease patients

	Number of medicine items									***Number of prescriptions***								
Phase		*Gender*		*Age group*			*Prescriber*				*Gender*		*Age group*			*Prescriber*		
	Total	*M*	*F*	*1*	*3*	*4*	*1*	*3*	*4*	***Total***	*M*	*F*	*1*	*3*	*4*	*1*	*3*	*4*
Phase 1	**575**	380	195	164	377	34	225	147	203	**305**	220	85	113	178	14	114	88	103
Phase 2	**384**	101	283	42	252	90	96	65	223	**260**	74	186	41	186	33	44	59	157
Biologics	***128***	*35*	*93*	*26*	*97*	*5*	*3*	*30*	*95*	***125***	*34*	*91*	*25*	*95*	*5*	*2*	*30*	*93*
Other	***256***	*66*	*190*	*16*	*155*	*85*	*93*	*35*	*128*	***135***	*40*	*95*	*16*	*19*	*28*	*42*	*29*	*64*
Phase 3	**301**	235	66	42	220	39	144	54	103	**140**	113	27	15	112	13	66	33	41

According to Table 4.7.5, the total number of medicine items and prescriptions claimed for Crohn's disease patients decreased from phase one (n = 575 medicine items and n = 305 prescriptions respectively) to phase two (n = 384 medicine items and n = 260 prescriptions) of their treatment. Based on Table 4.7.5, one third (33.33%) (n = 128) of the total number of medicine items 48% (n = 125) of all the prescriptions that were claimed during phase two was represented by biologic immunomodulators. The number of other medicine items and prescriptions (excluding biologics) claimed for Crohn's disease patients decreased further after treatment with biologic immunomodulators had stopped (phase three), since only 301 medicine items and 140 prescriptions were claimed for Crohn's disease patients during phase three of their treatment (refer to Table 4.7.5).

Based on Table 4.7.5, male patients received two thirds (66.09%) (n = 380) of the total number of medicine items, and more than two thirds (72.14%) (n = 220) of the total number of prescriptions claimed during phase one of Crohn's disease treatment. During phase two, however, 73.70% of the medicine items (n = 283) and 71.54% of all the prescriptions (n = 186) were claimed for female patients. Furthermore, 72.66% (n = 93) of biologics and 72.80% (n = 91) of the biologic prescriptions claimed during phase two were for female patients. After treatment with biologics, male patients once again received the larger percentage of the medicine items (78.07%) (n = 235) and prescriptions (80.71%) (n = 113) claimed. Thus, during the phases in which Crohn's disease patients did not receive biologic immunomodulators (phases one and three), male patients received more medicine items and prescriptions than females (almost double the quantity), whereas during the period in which patients did receive biologic immunomodulators (phase two), female patients received the largest percentage of the medicine items and prescriptions claimed (refer to Table 4.7.5).

The differences in the number of medicine items and prescriptions claimed for male and female Crohn's disease patients respectively and the changes thereof between the different phases of treatment are difficult to explain, because the type of medicine items claimed for males and females can differ, as can the composition of the prescriptions claimed for each gender group during each phase. Because the specific medicine items and the composition of the prescriptions claimed for male and female Crohn's disease patients were not investigated in this study, a logical and accurate explanation as to the reasons for changes in the percentages of medicine items and prescriptions represented by each gender group between the different phases of treatment could not be determined conclusively.

Crohn's disease patients between the ages of 40 and 64 years (age group three) received the largest percentage of the total number of medicine items (between 65% and 74%) and prescriptions (58% and 73%) claimed for Crohn's disease patients between 2005 and 2008 (refer to Table 4.7.5), which was expected since these patients represented the largest percentage of patients on the database (refer to Table 4.7.1). Before treatment with biologics, patients younger than 25 years (age group one) received the second largest percentage (28.52%) of all the medicine items (n = 164) and the prescriptions (n= 113) (37.05%) claimed, whereas Crohn's disease patients older than 64 years (age group four) received the smallest percentage of medicine items (5.9%) (n = 34) and prescriptions (4.59%) (n = 14) during phase one, which was predictable because age group one represented the second largest percentage of Crohn's disease patients and age group four represented the smallest percentage (refer to section 4.7.1). During phase two, however, the second largest percentage (23.44%) of the medicine items (n = 90) was claimed for patients older than 64 years, in contrast to phase one (refer to Table 4.7.5). There could be various possible reasons for this change in the number of medicine items suddenly represented by patients older than 64 years, such as changes in the composition of their prescriptions to accommodate the side-effects of the biologics, to name but one.

Furthermore, approximately 76% of all the biologics claimed during phase two of Crohn's disease treatment went to patients between the ages of 40 and 64 years, whereas approximately 20% were claimed for patients younger than 25 years, and only about 4% were claimed for patients older than 64 years. During phase three, the largest percentage of medicine items (73.09%) and prescriptions (80.00%) was still claimed for patients between the ages of 40 and 64 years, and as in phase one, the second largest percentage of the other prescriptions (10.71%) and medicine items (13.95%) was claimed for patients younger than 25 years (refer to Table 4.7.5), which was once again according to the patient distribution according to age (refer to section 4.7.1). .

When analysing the number of medicine items and prescriptions according to the type of prescriber, it is clear that more than a third (39.13%) of all the medicine items claimed during the first phase of Crohn's disease treatment, had been prescribed by general practitioners. The largest percentage of prescriptions (47.14%), as well as the largest percentage of medicine items (47.84%) claimed during phase three of the treatment had also been prescribed by general practitioners. However, during phase two of Crohn's disease treatment, when patients received biologic immunomodulators, 58.07% of all the medicine items and 60.38% of all the prescriptions were prescribed by the prescribers in group four (physiotherapists, immunologists, nephrologists, diabeticians and endocrinologists). Thus, during the periods in which Crohn's disease patients did not receive biologic immunomodulators, most of their prescriptions were from GPs, whereas during the time in which they did receive biologic immunomodulators, most of their prescriptions were form specialists.

According to Table 4.7.5, the number of medicine items and prescriptions claimed for Crohn's disease patients decreased from before to after treatment with biologic immunomodulators. In section 4.4.3.4 the focus is on ways in which the average number of medicine items per prescription per patient for Crohn's disease patients could have been affected by biologic immunomodulators.

4.4.3.4 Average number of medicine items per prescription per Crohn's disease patient

Table 4.7.6 summarises the average number of medicine items per prescription per Crohn's disease patient for each phase of his/her treatment between 2005 and 2008.

Table 4.7.6 Average number of medicine items per prescription per Crohn's disease patient

Phase		***Average number of items/Rx***	***Average number of items/Rx: Gender***		***Average number of items/Rx: Age***		
			Male	*Female*	*Age group 1*	*Age group 3*	*Age group 4*
Phase 1		1.84 ± 0.68	1.80 ± 0.25	1.87 ± 0.94	1.31 ± 0.23	1.98 ± 0.74	2.43 ± 0.00
Phase 2	*Biologics*	1.19 ± 0.30	1.27 ± 0.42	1.13 ± 0.18	1.39 ± 0.52	1.14 ± 0.18	1.00 ± 0.00
	Other	2.22 ± 1.95	1.33 ± 0.47	2.57 ± 2.26	1.00 ± 000	2.62 ± 2.49	3.04 ± 0.00
Phase 3		1.99 ± 0.73	2.16 ± 0.52	1.77 ± 0.97	1.69 ± 1.20	1.97 ± 0.13	3.00 ± 0.00

Table 4.7.6 indicates that there was not a big change in the average number of medicine items per prescriptions per patient from the period before (1.84 ± 0.68) to after (1.99 ± 0.73) treatment with biologic immunomodulators. The average number of biological medicine items per prescription per patient (1.19 ± 0.30) was significantly lower (*d*-value = 0.53) than the average number of medicine items per prescription that did not contain biologics (2.22 ± 1.95).

The average number of medicine items per prescription per patient did not differ much between male and female Crohn's disease patients during the first phase of treatment, but during phase two of Crohn's disease treatment, female patients received significantly more medicine items (excluding biologics) per prescription per patient (2.57 ± 2.26) than male patients (1.33 ± 0.47) (d-value = 0.55), but both male and female Crohn's disease patients rarely received more than one biologic immunomodulator per prescription. After treatment with biologics, male patients in turn received more other medicine items per prescription per patient (2.16 ± 0.52) than females (1.77 ± 0.97). The *d*-value (0.40) indicates that this difference in the average number of medicine items per prescription between males and females could have practical significance.

Table 4.7.6 further indicates that when treated with other medication (excluding biologics), patients older than 64 years (age group four) received the most medicine items per prescription per patient (2.43 ± 0.00 *phase one*; 3.04 ± 0.00 *phase two* and 3.00 ± 0.00 *phase three*), and patients younger than 25 years (age group one) received the smallest number of medicine items per prescription per patient (seldom more than one item per prescription per patient) (refer to Table 4.7.6). This ratio was, however, the other way around when Crohn's disease patients received biologic immunomodulators: even though the number of biologic immunomodulators per prescription seldom exceeded one, patients younger than 25 years received one more biological medicine items per prescription. The difference in the average number of biologics per prescription per patient between the different age groups one and four did have practical significance, as the *d*-value is 0.75 (refer to Table 4.7.6).

The difference in the average number of other medicine items per prescriptions per patient between age groups one and three also had practical significance (*d*-value = 4.87 *phase one* and 1.09 *phase three*), as did the difference in the average number of other medicine items per prescription between age groups two and three (*d*-value = 0.61 *phase one* and 7.92 *phase three*). Table A.35 in appendix B shows the average number of medicine items per prescription according to prescriber, but since these values are not *per patient*, this aspect will not be discussed in this section.

Table 4.7.6 thus showed that there was an increase in the average number of medicine items per prescription per patient between the first and third phases of Crohn's disease treatment. Section 4.4.3.5 will analyse the data in Tables A.33.1.1 to A.33.4.1 and A.34.1.1 and A.34.4.2 in appendix B to determine whether and in which ways the average cost per item and the average cost per prescription claimed for patients with Crohn's disease changed between the three phases of their treatment between 2005 and 2008.

4.4.3.5 Average cost per medicine item and prescription for Crohns' disease patients per phase

In this section follows a discussion of the data in Tables A.33.1.1 to A.33.4.2 and A.34.1.1 to A.34.4.2 in appendix B.

According to Table A.33.1.1 and A.34.1.1, the average cost per medicine item claimed during phase one of Crohn's disease treatment was R188.68 ± 166.19, whereas the average cost per prescription claimed for a Crohn's disease patients during this phase was (R355.70 ± 263.70).

The average cost per medicine item claimed for a Crohn's disease patient during phase two (R2986.76 ± 5319.79) was 1482.98% higher than the average cost per medicine item claimed during phase one, and the average cost per prescription (R4411.21 ± 7160.48) claimed during phase two of Crohn's disease treatment was also significantly higher than the average cost per prescription claimed during phase one. The median values however indicated that most of the medicine items (median = R 218.83) and prescriptions (median = R 1030.90) claimed during phase two did not have such high costs as the average indicated. Because high priced biological medicine items were also claimed during phase two, their considerable costs influenced the average medicine item and prescription cost rather considerably. When the average cost per medicine item and prescription for phase two were divided into the average cost of biologics and the average cost of other medication, could be seen that the average cost per biologic immunomodulator (R8660.69 ± 6052.28) as well as the average cost per biologic prescription (R8868.54 ± 8272.23) was significantly higher than the average cost per other medicine item (R149.70 ± 150.54) (median = R98.17) and prescription that did not contain biological medicine items (R284.05 ± 290.33) (median = R194.54). The average cost of biologics was thus ~5600% higher than the average cost of other medication claimed during the same phase (refer to Tables A.33.1.2 and A.34.1.2).

After treatment with biologic immunomodulators, the average cost per medicine item decreased to R170.00 ± 184.12 (median = R124.90), whereas he average cost per prescription increased to R365.50 ± 352.74. Thus, according to the average costs, there was a 2.76% increase in the average cost per prescription claimed before and after treatment with biologic immunomodulators, and there was a decrease of 10.99% in the average cost per medicine item claimed before and after treatment with biologic immunomodulators, but the median shows that the cost of most other medicine items increased with 27.23% from before (median = R98.17) to after (median = R124.90) treatment with biologics (refer to Table A.33.1.2).

- *Average cost per medicine item and prescription for Crohn's disease patients according to gender*

Based on Table A.33.2.1, the average cost per medicine item claimed for male Crohn's disease patients (R196.31 ± 167.88) during phase one was 12.95% higher than for female Crohn's disease patients (R173.81 ± 162.25), whereas Table A.34.2.1 indicates that the average cost per prescription was higher for females than for males. This could be because even though the medicine items claimed for females were less expensive, the combination in which the medicine items were claimed per prescription increased the average prescription cost.

During phase two of Crohn's disease treatment, the average cost per biologic immunomodulator (R8814.61 ± 6811.03) was 6.82% higher for a female patient than for male patients (R8251.69 ± 3325.82) and the average cost per biologic prescription claimed for a female patient (R9008.34 ± 9503.46) was 6.05% higher for a female than for a male patient (R8494.39 ± 3258.30) (refer to Tables A.33.2.2 and A.34.2.2).

The average cost per medicine item claimed for female Crohn's disease patients during phase three (R243.17 ± 308.10) increased with 39.91% from phase one, but the median (R102.38) shows that most of the medicine claimed for female patients decreased. The average cost per medicine item decreased with 31.35% for male Crohn's disease patients (R149.45 ± 123.12) over the same period. According to the average medicine item costs, the average cost per medicine item was 62.71% higher for females than for males, but the median values indicated that most of the medicine items claimed for females had a lower cost than those claimed for males (refer to Tables A.33.2.1 and A.34.2.1).

The average cost per prescription claimed for a female patient before (R398.74 ± 296.94) treatment with biologics was 17.59% higher than the average cost per prescription claimed for a male patient (R339.08 ± 248.42) during the same period. The only phase during which the difference in the average cost per prescription between males and females was sizeable, was during phase three. The average cost per prescription claimed for female patients after treatment with biologics (R594.41 ± 557.89) was 91.25% higher than the average prescription cost for a male patient (R310.80 ± 257.90). This difference rendered a *d*-value of 0.51 which indicated that the effect of the average cost per prescriptions for female patients after treatment with biologics had stopped, may be practically significant. The average cost per prescription for a female patient furthermore increased with 49.07% from phase one (before treatment with biologics) to phase three (after treatment with biologics), whereas the average cost per prescription for a male patient decreased with 9.10% during the same period (refer to Tables A.33.2.1 and A.34.2.1).

- *Average cost per medicine item and prescription for Crohn's disease patients according to age groups*

Table A.33.3.1 shows that during phase one of Crohn's disease patients, the average cost per medicine item was the highest for patients younger than 25 years (age group one) (R242.35 ± 205.86) when compared with the average cost per medicine item for patients between the ages of 40 and 64 years (age group three) (R172.79 ± 143.40) and the average cost per medicine item for patients older than 64 years (age group four) (R105.94 ± 112.07) (median = R51.33). According to Table A.34.3.1, the average cost per prescription claimed before treatment with biologics was the highest for patients between the ages of 40 and 64 years (R365.97 ± 262.87), whereas prescriptions claimed for patients older than 64 years during phase one had the lowest cost (R257.28 ± 339.06) (median = R) (refer to Table A.33.3.1). The reason for the higher prescription cost for patients in age group three could be because the composition of these patients' prescriptions caused a higher average prescription cost than for patients in age group one, even though the medicine items claimed for patients in age group one had a higher average cost than medicine items claimed for age group three (refer to Tables A.33.2.1 and A.34.2.1).

During phase two, the average cost per biologic immunomodulator was the lowest for patients older than 64 years (R5993.84 ± 0.00) and the highest for patients between the ages of 40 and 64 years of age (R8838.39 ± 6864.97). The average cost per biologic prescription (Table A.34.3.2) was the lowest for patients older than 64 years (R5993.84 ± 0.00) and the

highest for patients between 40 and 64 years (R9024.46 ± 9444.17). The difference in the average cost per prescription between the different age groups is not practically significant (*d*-values below 0.2) (refer to Tables A.33.3.2 and A.34.3.2).

After treatment with biologic immunomodulators, the average cost per medicine item decreased with 139.10% (R101.36 ± 153.76) for Crohn's disease patients in age group one, but the median (R11.06) showed that the cost of most of the medicine items claimed for patients younger than 25 years decreased with 1990.42% from phase one to phase three. The average cost per medicine item increased with 7.28% for patients in age group three (R185.37 ± 191.61) (median = R150.23), and with 48.40% for patients in age group four (R157.22 ± 154.17) (median = R102.38). The average cost per medicine item before treatment with biologic immunomodulators (phase one) was thus the highest for age group one, but the average cost per medicine item after treatment with biologic immunomodulators (phase three) was the highest for Crohn's disease patients in age group three (refer to Table A.33.3.1). The average cost per prescription claimed for patients in age group four (R471.66 ± 464.38) during phase three increased with 83.33% from phase one. Consequently prescriptions claimed for patients older than 64 years during phase three became the prescriptions displaying the highest average cost. The average cost per prescription for patients aged between 25 and 39 did not change much from before treatment with biologics to after (R364.11 ± 350.15). However, the average cost per prescription for patients younger than 25 years decreased with 19.31% from phase one to phase three (refer to Table A.34.3.1).

- *Average cost per medicine item and prescription for Crohn's disease patients according to prescriber*

When the average cost per medicine item was compared between different prescribers, Tables A.33.4.1 and A.34.4.1 indicate that medicine items and prescriptions prescribed for Crohn's disease patients by specialists in prescriber group four had a higher average cost when compared to the average cost per medicine item and prescription prescribed by a general practitioner. The average cost per medicine item (R190.85 ± 162.47) and prescription (R376.14 ± 259.60) prescribed by a specialist before treatment with biologic immunomodulators was ~24% higher than medicine items (R153.25 ± 129.22) and prescriptions (R302.46 ± 244.12) prescribed general practitioners (refer to Tables A.33.4.1 and A.34.4.1).

After treatment with biologic immunomodulators, the average cost per medicine item (R156.38 ± 143.73) and prescription (R392.85 ± 314.45) prescribed by a group four specialist was 32.74% lower than the average cost per medicine item (R207.58 ± 218.00) (median = R165.27) and prescription prescribed (R452.90 ± 398.55) by a general practitioner. Furthermore, the average cost per prescription prescribed by a general practitioner increased with 49.74% between phases one and phase three, whereas the average cost per prescription prescribed by a specialist increased with 4.44%. The difference in the average cost of other medicine items and prescriptions prescribed before and after treatment with biologic immunomodulators between the different prescriber types was not practically significant (*d*-values less than 0.2) (refer to Tables A.33.4.1 and A.34.4.1).

Based on Tables A.33.4.2 and A.34.4.2, the average cost per biologic immunomodulator was significantly higher when prescribed by a general practitioner (R44306.79 ± 0.02) than when prescribed by a specialist (R7706.81 ± 2763.24) (*d*-value = 13.25). The average cost per biologic prescription prescribed by a general practitioner (R66460 ± 31329.61) (median = R66460.18) was significantly higher (*d*-value = 1.87) than the average cost per biologic prescription prescribed by a specialist (R7872.55 ± 2824.39) (median = R8571.09). The exceptionally high average cost per biologic prescription prescribed by a general practitioner could be explained by the notion that the entire treatment regime with biologics was claimed on one occasion for one Crohn's disease patient, which could cause a dramatic increase in the average prescription and medicine item cost.

When the *d*-value is calculated between the average cost per medicine item (R2986.76 ± 5319.79) and prescription (R4411.21 ± 7160.48) claimed for a Crohn's disease patient during phase two and the average cost per medicine item claimed in phases one and three, a value of 0.53 is obtained. This indicates that the effect size of medicine items claimed during phase two of Crohn's disease treatment is medium, but when the *d*-value between the average cost per biologic immunomodulator (R8660.69 ± 6052.28) and other medicine items is calculated (both claimed during phase two), a value of 1.41 is obtained, which indicates that the impact of biologic immunomodulators is large and practically significant (refer to Tables A.33.4.2 and A.34.4.2).

The analysis of the average cost per medicine item and the average cost per prescription indicates that biologics used in the treatment of Crohn's disease were relatively expensive. Table 4.7.7 (compiled from Tables A.36.1 to A.36.3 in appendix B) shows the average number of biologic prescriptions claimed per Crohn's disease patient over the study period as to try and determine the average cost of these therapies during a four-year period.

Table 4.7.7 Average number of biologic prescriptions per Crohn's disease patient within the four-year study period

Average number of Rx per patient	*Average number of Rx/patient: Gender*		*Average number of Rx/patient: Age*		
	Male	*Female*	*Age group 1*	*Age group 3*	*Age group 4*
11.36 ± 11.22	6.80 ± 8.84	15.17 ± 12.29	8.33 ± 6.35	13.57 ± 13.39	5.00 ± 0.00

Based on Table 4.7.7, Crohn's disease patients received an average of 11.36 ± 11.22 biologic prescriptions per patient during the four-year study period. Female Crohn's disease patients received almost twice as many biologic prescriptions (15.17 ± 12.29) per year as the number of biologic prescriptions claimed for male patients (6.80 ± 8.84) during the four-year period. Patients between 40 and 64 years received the most biologic prescriptions per patient (13.57 ± 13.39), whereas patients older than 64 years (age group four) received a smaller number of biologic prescriptions (5.00 ± 0.00) per patient during the four-year period. Patients with Crohn's disease younger than 25 years between 2004 and 2008 received an average of 8.33 ± 6.35 biologic prescriptions per patient per year.

According to Table 4.7.7, patients with Crohn's disease thus received approximately two to three prescriptions for biologic immunomodulators per year, depending on their gender and age, which was not exceptionally often. But, since the costs of these items were exceptionally high, Table 4.7.8 indicates to which extent the treatment cost with these agents can be influenced, and in which way such treatment exercises an impact on the treatment cost of other medication.

4.4.3.6 Analysis of the total medicine treatment cost of Crohn's disease per phase

Table 4.7.8 (compiled from Tables A.33.1.1 to A.34.4.2 in appendix B) shows how the total medicine cost of Crohn's disease changed across the three phases of treatment.

Biologic immunomodulators claimed for Crohn's disease patients represented 0.015% (R1, 108,568.02) of the total cost of all medicine items (R7, 483,759,176.23) claimed through the PBM during the four-year period. Biologic immunomodulators represented 84.85% of the total medicine treatment cost (cost of all three phases) of Crohn's disease patients (R1, 306,572.75) between 2005 and 2008, whereas other medication claimed in conjunction with biologic immunomodulators represented 2.93% of the total medicine cost of Crohn's disease patients.

Table 4.7.8 Total medicine treatment cost of Crohn's disease per phase

	Total medicine treatment cost									
Phase	**Variables**		***Gender***		***Age group***			***Prescriber***		
		Total	*Males*	*Females*	*1*	*3*	*4*	*1*	*3*	*4*
Phase 1	Total	**108,489.52**	74,596.75	33,892.77	39,744.91	65,142.69	3,601.92	34,480.22	35,267.02	38,742.28
	Medical aid scheme	104,144.17	72,768.35	31,375.82	38,687.45	62,747.26	2,709.46	32,531.15	34,880.20	36,732.82
	Patient	4,345.35	1,828.40	2,516.95	1,057.46	2,395.43	892.46	1,949.07	386.82	2,009.46
Phase 2	Total	**1,146,914.34**	295,961.31	850,953.03	229,354.63	877,181.02	40,360.69	143,227.48	252,621.60	751,065.26
	Medical aid scheme	1,117,576.68	291,277.96	826,298.72	229,354.63	850,033.57	38,188.48	141,602.38	252,547.90	723,426.40
	Patient	29,337.66	4,683.35	24,654.31	0.00	27,165.45	2,172.21	1,625.10	73.70	27,638.86
Biologics	Total	**1,108,568.02**	288,809.23	819,758.79	221,275.39	857,323.43	29,969.20	13,2920.36	243,500.43	732,147.23
	Medical aid scheme	1,084,700.96	284,319.81	800,381.15	221,275.39	833,456.37	29,969.20	13,2920.36	243,500.43	708,280.17
	Patient	23,867.06	4,489.42	19,377.64	0.00	23,867.06	0.00	0.00	0.00	23,867.06
Other	Total	**38,346.32**	7,152.08	31,194.24	8,079.24	19,857.59	10,391.49	10,307.12	9,121.17	18,918.03
	Medical aid scheme	32,875.72	6,958.15	25,917.57	8,079.24	16,577.20	8,219.28	8,682.02	9,047.47	15,146.23
	Patient	5,470.60	193.93	5,276.67	0.00	3,298.39	2,172.21	1,625.10	73.70	3771.80
Phase 3	Total	**51,169.41**	35,120.23	16,049.18	4,257.07	40,780.71	6,131.63	29,891.70	5,170.69	16,107.02
	Medical aid scheme	47,276.43	32,507.74	14,768.69	2,550.39	39,859.21	4,866.83	29,310.13	4,628.70	13,337.60
	Patient	3,892.98	2,612.49	1,280.49	1,706.68	921.50	1,264.80	581.57	541.99	2,769.42

Based on Table 4.7.8, other medication claimed for Crohn's disease patients before starting treatment with biologics represented 8.30% (R108, 489.52) of the total medicine cost of Crohn's disease patients, whereas those claimed after treatment with biologics represented 3.92% (R51, 169.41).

Based on Table A.33.1.1 in appendix B, the total amount spent on biologic immunomodulators represented 96.66% (R1, 108,568.02) of the total medicine cost of phase two (R1, 146,914.34), but the biologic immunomodulators only represented 33.33% (n = 128) of all the medicine items claimed during that phase. When the CPI of biologic immunomodulators is calculated by dividing the percentage cost (96.66%) by the percentage frequency (33.33%), a value of 2.9 is obtained. Since this value is greater than one, it indicates that biologic immunomodulators were relatively expensive.

However, according to Table 4.7.8, the total cost of treatment (with other medication) of Crohn's disease decreased with 112.02% from before to after treatment with biologic immunomodulators.

Section 4.4.3.5 indicated that the average cost per medicine item and the average cost per prescription for Crohn's disease patients increased from phase one to phase three, whereas section 4.4.3.6 indicated that the total medicine treatment cost of Crohn's disease decreased from before to after treatment with biologic immunomodulators.

However, once again, these values were for the average cost per prescription and average cost per medicine item *per phase.* Therefore, the average cost per medicine item *per patient* and the average cost per prescription *per patient* will also be discussed in order to determine possible differences with regard to the average cost per item (or prescription) *per phase* and the average cost per item (or prescription) *per patient.*

4.4.3.7 Analysis of the average cost per medicine item per patient and average cost per prescription per Crohn's disease patient

As shown in Table 4.7.4, there were eleven Crohn's disease patients who received biologic immunomodulators between 2005 and 2008. Based on Table 4.7.9, all eleven patients received other medicine items and prescriptions before starting treatment with biologic immunomodulators. During phase two, all of these eleven Crohn's disease patients received biologic immunomodulators, but only seven (63.64%) received other medicine items (excluding biologics) during the same phase. After treatment with biologic

immunomodulators had stopped, only nine (81.82%) of the patients still received other medicine items through the PBM. This indicates that four (36.36%) patients did not receive adjunctive therapy during phase two of Crohn's disease treatment and that two (18.18*) patients either stopped treatment after phase two of the treatment altogether, or left the medical aid scheme.

Table 4.7.9 Average cost per medicine item and prescription per Crohn's disease patient

Average cost per medicine items per patient					
Phase		Patients	Total cost per Rx	Medical aid scheme	Levy
Phase 1		11	172.54 ± 109.05	165.96 ± 111.17	6.58 ± 7.59
Phase 2	***Biologics***	11	10742.71 ± 11338.81	10669.88 ± 11370.29	72.84 ± 181.81
	Other	7	263.95 ± 176.38	248.33 ± 188.72	15.62 ± 20.01
Phase 3		9	257.74 ± 143.98	247.60 ± 155.00	10.14 ± 16.0
Average cost per prescription per patient					
Phase		Patients	Total cost per Rx	Medical aid scheme	Levy
Phase 1		11	172.70 ± 109.11	166.11 ± 111.22	6.59 ± 7.59
Phase 2	***Biologics***	11	10742.71 ± 11338.81	10669.88 ± 11370.29	72.84 ± 181.81
	Other	7	263.95 ± 176.38	248.33 ± 188.72	15.62 ± 20.01
Phase 3		9	257.74 ± 143.98	247.60 ± 155.00	10.14 ± 16.07

As it can be seen in Table 4.7.9, the average cost per medicine item per patient as well as the average cost per prescription per patient for Crohn's disease patients appeared as very nearly the same for all three phases of their treatment during the four-year study period, which could probably be ascribed to the fact that there were so few Crohn's disease patients on the database between 2005 and 2008 who received biologics. Therefore, the results of this section will only be discussed in terms of the average cost per prescription per patient.

During the first phase of treatment, the average cost per prescription per Crohn's disease patient was R172.70 ± 109.11, of which 96.18% was paid by the medical aid scheme, and 3.82% was co-paid by the patient. During phase two (when Crohn's disease patients received biologic immunomodulators), the average cost per prescription per patient increased significantly (*d*-value = 0.93) (refer to Table 4.7.9).

Not only was the average cost per prescription per patient (R10742.71 ± 11338.81) (median = R8541.25) for a prescription that contained biologic immunomodulators 3969.98% higher than the average cost per prescription per patient for prescriptions that did not contain

biologics (claimed before treatment with biologics), but the average cost per prescription per patient for other prescriptions (R263.95 ± 176.38) claimed during phase two was also 52.84% higher than the average cost per prescription per patient claimed before treatment with biologics. The median, however, shows that the cost of most biologic prescriptions (R8541.25) was 3135.93% higher than the cost of other prescriptions claimed during phase two. During phase two, the medical aid scheme paid 99.32% of the total prescription cost for a biologics prescription, and 94.08% of the total prescription cost for a non-biologic prescription (refer to Table 4.7.9).

The average cost per prescription per Crohn's disease patient claimed during phase three (R257.74 ± 143.98) decreased with 4068.04% from phase two when compared to the average cost per prescription per patient for a biologics prescription, and with 2.41% when compared to other prescriptions (refer to Table 4.7.9). However, the average cost per prescription per patient for other prescriptions (excluding biologics) increased with 49.24% from before (R172.70 ± 109.11) treatment with biologics to after (R257.74 ± 143.98) treatment with biologics. The medical aid scheme paid 97.07% of the total prescription cost during phase three and the patient co-paid the remaining 3.93% (refer to Table 4.7.9).

Thus, the average cost of medicine treatment per patient was significantly higher in the period during which Crohn's disease patients received treatment with biological immunomodulators. However, based on Table 4.7.8, treatment with biologics seemed to decrease the total medicine treatment cost of Crohn's disease. Together with the increase in the average prescription cost, the average scheme amount for other prescriptions increased with 49.06% from before to after treatment with biologics, and the average patient levy increased with 53.87% (refer to Table 4.7.9).

4.4.3.8 Summary of analysis of Crohn's disease patients

During this study period, there were only eleven patients with Crohn's disease on the PBM database who received biologic immunomodulators (i.e. adalimumab, etanercept, infliximab) between 2005 and 2008. Crohn's disease patients represented 1.5% of the total number of patients (n = 713) who claimed at least one of the six biologics investigated in this study between 2005 and 2008 (refer to Figure 3.1). There was only one more female patient with Crohn's disease than males, which is in accordance with the literature, which states that males and females are equally affected by this disease (refer to section 2.7.2.2). Most of the patients on the PBM database who had been diagnosed with Crohn's disease were between

40 and 64 years of age, which also corresponds with the literature, that states that mainly adults are affected by Crohn's disease (refer to section 2.7.2.2).

The average cost of medicine items and prescriptions claimed for Crohn's disease patients increased from before to after treatment with biologic immunomodulators (refer to section 4.4.3.5), as did the average number of medicine items per prescription per patient (refer to section 4.4.3.4). The total number of medicine items and prescriptions claimed for these patients, however, decreased considerably from before treatment with biologics to afterwards (refer to section 4.4.3.3), and in doing so contributed to a decrease in the total medicine treatment cost of Crohn's disease from phase one to phase three.

The increase in the average cost of medicine items and prescriptions may, however, be ascribed to the inevitable increase in the cost of consumer products and medical inflation, since this analysis was done across a four-year period and price increase could be expected. Yet, when medical aid schemes agree to spend thousands of rand on a single patient for biological treatment, they would expect both effectiveness and efficacy, and the total treatment cost of Crohn's disease seemed to be decreased after these patients had been treated with biologic immunomodulators. However, treatment outcomes were not measured in this study and the impact of biological therapies on Crohn's disease patients was not established. Furthermore, the composition of prescriptions claimed for Crohn's disease patients before and after treatment with biologics was also not investigated, and therefore it is difficult to establish exactly why the number of medicine items and prescriptions claimed for Crohn's disease patients decreased from phase one to phase three of their treatment.

4.5 Chapter summary

Chapter four presented the results of the empirical investigation of this research project. The cost and prevalence of biological medicine were analysed and discussed, together with the prevalence and cost of other medication (excluding biologics) claimed by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease.

In chapter five the conclusions drawn from the study as well as the limitations and recommendations for the study will be discussed.

CHAPTER 5

Conclusions and Recommendations

Chapter five stipulates the conclusions drawn from this research project and lists recommendations for this study. The conclusions and recommendations discussed in this chapter are based on the results of the empirical investigation and literature review. Conclusions will be directed according to the specific objectives stated in chapter one. The factors that limited the scope and applicability of the study will also be stated.

5.1 Conclusions

Ten specific objectives were stated in Chapter one, of which five specific objectives were stated for the literature review and five specific objectives were stated for the empirical investigation.

- **Specific objective one was to *conceptualise the immune system and its responses and components involved in the pathogenesis of autoimmune diseases from available literature*.**

From the literature it was established that the immune system is a complex organisation of specialised cells and molecules designed to protect the host (i.e. the human body) from infection and disease (refer to section 2.1). According to the literature, immune cells normally respond to and destroy foreign antigens and pathogens that enter the body, in what are called “normal immune responses”, but sometimes these cells respond strangely, in what is called “abnormal immune responses” (refer to section 2.2). In abnormal immune responses, immune cells may attack and damage the host’s own cells. This is referred to as “autoimmunity”. When the body launches an attack on its own cells, autoimmune diseases arise, e.g. rheumatoid arthritis, multiple sclerosis, lupus erythematosus (refer to section 3.3).

- **Specific objective two was to *conceptualise "biologics" from available literature.***

For the purpose of this study, biologics were defined and classified from available literature and a brief overview of biologics was given.

It was difficult to find a comprehensive definition for biologics (or biological medicine) that was universally precise and coherent, because the term "biologics" is used by different areas of discipline and the definition varies depending on the context in which it is used (refer to section 1.1). It was, however, established that regardless of a precise definition, the term biologics generally refers to any product derived from *living organisms and tissues* indicated for diagnostic or therapeutic application in diseases (refer to section 1.1). The definitions provided by the South African Medicine Control Council (MCC) and the American Food and Drug Association (FDA) were chosen as the operational definitions for biologics for the purpose of the study, which stated that biologics are *medicine where the active ingredient and/or any of the inert substances have been derived from living organisms or tissues, or manufactured using a biological process, and that replicate natural substances in the human body such as enzymes, antibodies, or hormones* (refer to section 1.1).

Biologics were furthermore classified (for the purpose of this study) from available literature. As for a definition, it was difficult to find an accurate, comprehensive and inclusive classification of "biologics" that included all of the biologics relevant to this study. The classifications of these products provided in South African literature (MIMS and SAMF) did not include all of the biologics studied in this dissertation in one pharmacological group. The WHO's ATC classification system on the other hand did classify all the therapeutic biologics investigated in this study as "antineoplastics and immunomodulators" (group L), but this group also encompassed a wide range of other medicine items not relevant to this study (refer to section 2.5.1). The FDA's classification system of therapeutic biologics was therefore used as the operational classification for biologics, since the CDER and the CBER within the FDA regulate and license these products. When a medicine product is defined as a therapeutic biologic, the CDER adds it to their list of licensed therapeutic biologics, together with its licensed indication for use. This list provided by the CDER was used as the source of all the biologics registered and licensed for use in humans. Those biologics available in South Africa and indicated for autoimmune diseases were selected for further investigation (refer to section 2.5.2). The classification of biologics in this study was thus based on *the indication of use* of *any medicine item licensed as a therapeutic biologic.* The relevant biologics identified from this classification were then verified through the medicine claims database and then classified according to the ATC and MIMS classifications.

- **Specific objective three was to *conceptualise the usage patterns of biologics in South Africa from available literature*.**

From the literature it was clear that biologics are currently indicated to treat mostly chronic, long-term, hard-to-treat and/or life-threatening diseases, that include widespread conditions like cancers, autoimmune diseases (i.e. rheumatoid arthritis, multiple sclerosis, psoriasis, asthma etc.), rare or serious diseases (i.e. HIV/AIDS, Fabry disease, Gaucher disease etc.), heart diseases, coronary and blood diseases, organ transplants and a few other hard-to-treat diseases (i.e. cystic fibrosis, severe sepsis, etc.) (refer to section 2.5.3).

Literature on the prevalence of biologics in South Africa was difficult to find. Data from one South African pharmacy benefit management company, Mediscor PBM, however, showed that biological medicine items represented only about 2% of the total number of medicine items claimed through the PBM in 2008 (refer to section 2.5.4). This data, however, only represent a section of the private health care sector of South Africa, and might not be a direct representation of the total prevalence of biologics' use in South Africa, but it gives the idea that the frequency of the use of biologics in a section of the private health care sector of South Africa is relatively low.

- **Specific objective four was to *investigate the usage patterns of biologics in the treatment of autoimmune diseases, while focusing on rheumatoid arthritis, multiple sclerosis and Crohn's disease, and determine the pre-usage requirements of biologics in these diseases*.**

It was established through a literature review that eighteen biologics had been approved by the FDA's Center of Drug Evaluation and Research (CDER) for the treatment of autoimmune diseases in humans during the time of this study (FDA, 2009b) (refer to Table 2.9). Thirteen of these biologics were licensed by the FDA for use in multiple sclerosis, rheumatoid arthritis and/or Crohn's disease (according to FDA, 2009b), but only six of the thirteen biologics were available and licensed for use in South Africa (according to Snyman, 2010) and also available on the medicine claims database (refer to Table 2.10), namely *adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b* and *rituximab* (refer to section 2.6). From South African literature (i.e. Rossiter, 2010; Snyman, 2010) the licensed indications of these six biologics (for use in South Africa) were also determined, and *adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b* and *rituximab* were established as those biologics used in the treatment of rheumatoid arthritis; multiple sclerosis

and Crohn's disease in South Africa (refer to section 2.6). From the literature it was determined that adalimumab and infliximab are indicated to treat (among other autoimmune diseases) rheumatoid arthritis and Crohn's disease, etanercept is primarily indicated to treat rheumatoid arthritis, whereas the beta interferons are indicated to treat multiple sclerosis (refer to section 2.7). The use of these biologics in rheumatoid arthritis, multiple sclerosis and Crohn's disease was discussed comprehensively in the literature (refer to section 2.7), together with the other medication (excluding biologics) used in the treatment of each of the selected autoimmune diseases. There are, however, pre-usage requirements for biologics.

The pre-usage requirements of biologics in rheumatoid arthritis, multiple sclerosis and Crohn's disease were determined from the literature. Patients who have been diagnosed with rheumatoid arthritis must fulfil the criteria set by the South African Rheumatoid Arthritis Association (SARAA) before they are permitted to use biological medicine (refer to section 2.7.1.7) and any rheumatoid arthritis patient who is to use biological medicine must be registered with the SARAA biologics registry first (refer to section 2.11). The use of biologics in Crohn's disease and multiple sclerosis is also reserved as a last resort. Patients who are diagnosed with Crohn's disease or multiple sclerosis must first be treated with the traditional therapies as depicted by the treatment algorithms, and only when patients have exhausted all possible treatments without an adequate response do they qualify for biological medicine treatment (refer to Figure 2.14 in section 2.7.2.6 and Figure 2.15 in section 2.7.3.6).

- **Specific objective five was to *conceptualise the economic impact of biologics on the cost of health care*, and to *investigate the legislation surrounding the payment of biologics and the issues surrounding generics*.**

When their cost is taken into consideration, biologics fall into the category of "specialty pharmaceuticals", which are by and large considered to be high priced medication indicated for the treatment of chronic or serious diseases (refer to section 2.9.1). Even though the prevalence of use of specialty pharmaceuticals is currently relatively low, it is rapidly on the rise as more biologics enter the pharmaceutical market and additional indications are found for the existing ones, which contributes to the biologics medicine market being the fastest growing sector of the pharmaceutical marketplace (refer to section 2.9.1).

According to the literature, the rheumatoid arthritis biologics Enbrel® (etanercept), and Humira® (adalimumab) and the cancer/rheumatoid arthritis drug MabThera® (rituximab) were three of the top fifteen medicine items that contributed to the increase in global health care expenditure between 2006 and 2008, and during this time, the global sales of these

biological autoimmune agents increased dramatically (refer to section 2.9.2). In South Africa, a pharmacy benefit management company, Mediscor PBM, also indicated the impact of biological medicine on their total annual medicine expenditure, when they reported that the biological cancer agents (i.e. rituximab and trastuzumab) represented the third largest percentage of the total medicine expenditure of 2008, even though these agents only represented 1.7% of the total number of medicine items claimed through the PBM that year. The biologics indicated for rheumatoid arthritis (Enbrel® and MabThera®) were also two of the top 50 cost drivers between 2006 and 2008, and even though only 0.01% of the PBM's beneficiaries used Enbrel®, it contributed to 0.3% of the total annual medicine expenditure of the PBM (refer to section 2.9.2). The cost-prevalence index of Enbrel® in 2008 was 30, which indicates that the impact of these therapies is large, and that they are relatively expensive.

The legislation surrounding the reimbursement of biological medicine by medical aid schemes in South Africa was also investigated. It was established from the South African Council for Medical Schemes (CMS) that medical aid schemes are only required to reimburse those medicines included in the treatment algorithm of a disease, in other words, medicine treatment equal to that provided in the state sector. Since the state sector does not make biologics available to their patients, medical aid schemes may refuse to pay for biologics when treatment with the standard therapies in the treatment algorithm is adequate. However, when a patient has reached the end of a specific disease's treatment algorithm and had failed to respond to the standard treatments, his/her medical aid scheme had to pay for additional treatment (if the patient's physician could prove that standard treatment had been ineffective). Thus, South African Medical Aid schemes are only obligated to reimburse biological medicine indicated for rheumatoid arthritis, multiple sclerosis or Crohn's disease when patients have been treated with the standard treatments in the treatment algorithms, but without responding adequately (refer to section 2.11).

It was furthermore established that no generic equivalents for biological medicines were currently available. It was first of all determined that the term "generic" should not be applied to biologics, since identical copies of biologics cannot be made. The terms "biosimilars" or "follow-on biologics" should be used (refer to section 2.10), because "biosimilars" accurately describes biological products alleged to have the same properties as original biologics, but without being identical (refer to section 2.10). Apart from the science that complicates the development of biosimilars, it was determined that there were currently also no regulatory processes or legislation in place for follow-on biologics (refer to section 2.10). This suggests

that even if accurate biosimilars could be developed, it would be a while before they would reach the market.

- **Specific objective six was to *analyse the current prescribing patterns and cost trends of biologic immunomodulators in a section of the private health care sector of South Africa by using a medicine claims database for the period 2005 to 2008.***

- *The prevalence of use of biologic immunomodulators in a section of the private health care sector of South Africa according to demographic parameters.*

Overall, the results obtained from the study indicated that the number of patients on the total database who received biologics between 2005 and 2008 were in the minority, since not even 0.1% (n = 713) of the total patient population of the database received biologic immunomodulators over the four year study period (refer to Figure 3.1). As a result, the number of biological medicine items and prescriptions claimed between 2005 and 2008 were also in the minority when compared to the total number of medicine items and prescriptions claimed through the PBM. The study results showed that biologic immunomodulators (i.e. adalimumab, etanercept, infliximab, interferon beta-1a and interferon beta-1b, and rituximab) represented only 0.016% (n = 11,914) of the total number of medicine items and only 0.03% (n = 9,357) of the total number of prescriptions claimed through the PBM over the four-year study period (refer to section 3.3.2).

It was, however, determined that the number of patients who received biologics increased with 0.024% from 2005 to 2008, and the percentage medicine items and prescriptions represented by biologic immunomodulators increased with 0.014% and 0.031% respectively from 2005 to 2008 (refer to section 4.3.1.1). This implies that the prevalence of use of biological medicine items in a section of the private health care sector of South Africa was *increasing*.

More than two thirds of the patients who received biologic immunomodulators between 2005 and 2008 were female, which was corresponding with the gender distribution of the patient population of the total database, of which ~55% was represented by females and ~44% was represented by males over the study period. Consequently, about two thirds of all biologic immunomodulators were claimed for female patients, which indicates that the prevalence of use of biologic immunomodulators in a section of the private health care sector of South Africa was greater among females than males (refer to section 4.3.2.1).

The patient distribution of the total database according to age indicated that over the four-year study period, the largest percentage of the patient population of the total database was

represented by patients between the ages of 40 and 64 years (refer to section 4.3.3.1). The analysis of the biologic immunomodulators portrayed the same results, as more than half of the patients who received biologic immunomodulators between 2005 and 2008 were between the ages of 40 and 64 years of age, followed by patients aged 65 years and older (refer to section). Consequently, the majority (~80%) of biologic immunomodulators had been claimed for patients older than 39 years, most of who had been between 40 and 64 years of age between 2005 and 2008 (refer to section 4.3.3.2). This suggests that the prevalence of use of biologic immunomodulators in a section of the private health care sector of South Africa was greater among older patients (> 39 years).

In conclusion and according to the results obtained from the study it was determined that the frequency of use of biologic immunomodulators in a section of the private health care sector of South Africa is very low. At the same time it was determined that the use of biologic immunomodulators has shown an increased frequency over time. It was furthermore determined that the prescribing of biologic immunomodulators according to demographic parameters, was the greatest among females between the ages of 40 and 64 years of age in a section of the private health care sector of South Africa.

- *The current cost of biologic immunomodulators in a section of the private health care sector of South-Africa, and how the cost of biologics compare to the cost of other medicine.*

The study results indicated that biologic immunomodulators were used far less often (< 0.1%) than other medicine items (excluding biologics) over the study period. This was revealed when the total number of medicine items claimed through the PBM over the four-year study period was taken into account. As a result, the cost associated with these medicine items was marginal compared to the total annual medicine cost over the four-year period (refer to section 4.3.1.3). From the results obtained from the study it was determined that biologic immunomodulators contributed to 1.28% of the total medicine expenditure of the PBM between 2005 and 2008 (refer to section 4.3.1.3). However, when the cost-prevalence index (CPI) was determined for these medicine items, a CPI of 42.67 was obtained when the percentage cost (1.28%) was divided by the percentage frequency of biologic prescriptions (0.03%), and a CPI of 80 was obtained when the percentage cost was divided by the percentage frequency of biological medicine items (0.016%). Thus, even though biologic immunomodulators do not currently contribute to a great percentage of the overall medicine

expenditure in a section of the private health care sector in South Africa, these medicine items are relatively expensive.

The current average cost of biologic immunomodulators is significantly higher in comparison with average cost of other medicine items. The study results indicated that the average cost per biological medicine item was ~5600% higher than the average cost per other non-biological medicine item in 2005, and ~8700% higher in 2008. The *d*-value (1.6) between the average medicine item cost of a biological medicine item and a non-biological medicine item indicates that the size of the effect of biological therapy is large and practically significant (refer to section 4.3.1.2). In addition, it was determined that there had been a 71.10% increase in the average cost per biological medicine item from 2005 to 2008, which was significant when compared with the increase in the average cost of other medicine items (16.41%) over the same period. The increase in the costs of medicine items is inevitable, due to (amongst other reasons) increases in the consumer price index and medical inflation, but the increase in the cost of biological medicine items is more than 50% greater than the increase in the cost of other medicines.

Thus, not only is the current cost of biologic immunomodulators in a section of the private health care sector of South Africa extremely high, but the cost of these medicine items is also *increasing* over time.

- **Specific objective seven was to *analyse how biologic immunomodulators influence medicine expenditure of medical aid schemes in a section of the private health care sector of South Africa over time.***

From the results obtained from the data it was established that the total expenditure on biological medicine claimed through the PBM *quadrupled* in four years' time (n = R9, 855,161.01 in 2005; n = R35, 766,286.42 in 2008) (refer to section 4.3.1.2), which indicates that the expenditure on biologic immunomodulators in a section of the private health care sector of South Africa is rapidly *increasing*.

The impact of the cost of biologic immunomodulators on *medical aid schemes* in a section of the private health care sector of South Africa becomes apparent when it is considered that medical aid schemes reimbursed between 96% and 98% of the total cost of biological medicine items each year, which implies that the total amount spent on biologic immunomodulators by medical aid schemes also quadrupled from 2005 to 2008 (refer to section 4.3.1.4). Furthermore, the contribution of the medical aid scheme to the total cost of

biological medicine items increased from 2005 to 2008 (with ± 2%), whereas the contribution of the medical aid scheme to the total cost of medicine items on the total database decreased with ± 6% during the same period (refer to section 4.3.1.4). The reason for the decrease in the medical aid scheme contribution to the total cost of other medication could be ascribed to the notion that medical aid schemes are shifting the cost burden of medicine to their patients because of rising health care costs and a constrained fiscus due to global and regional recessions. From the results it was determined that medical aid schemes spent almost R100 million (n = R93, 327,876.76) on biologic immunomodulators between 1 January 2005 and 31 December 2008 in a section of the private health care sector of South Africa. This amount, however, represented only 1.46% of the total expenditure on medication (n = R6, 394,712,862.63) by medical aid schemes over the four-year period, which could signify that the impact of biologic immunomodulators on medical aid schemes was inconsequential (refer to section 4.3.1.4).

However, the CPI (42.67 for biologic prescriptions and CPI 80 for biological medicine items) indicated that biologic immunomodulators are relatively expensive. Since more than 96% of the total cost of biologic immunomodulators is reimbursed by medical aid schemes, it is logical that the impact of biologic immunomodulators on medical aid schemes is large. Furthermore, it seems that the impact of biologics on medical aid schemes will continue to grow, since the cost and prevalence of these medicine items increases each year.

- **Specific objective eight was to *determine the prescribing patterns of biologic immunomodulators in the treatment of rheumatoid arthritis, multiple sclerosis or Crohn's disease.***

The results obtained indicated that there were 713 patients on the total database who claimed biological medicine items (i.e. adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b and rituximab) through the PBM between 2005 and 2008 (refer to section 3.3.2). From the results it was determined that 45.44% (n = 324) of these patients were diagnosed with rheumatoid arthritis, multiple sclerosis or Crohn's disease during the study period (refer to section 3.3.2), which is an indication that the greater percentage (~55%) of patients who received biologic immunomodulators during the four-year period received them to treat other diseases (i.e. cancer etc.) than the three investigated in this dissertation. Out of the 324 patients on the database who received biologic immunomodulators for rheumatoid arthritis, multiple sclerosis, or Crohn's disease, most had multiple sclerosis (n = 172), followed by rheumatoid arthritis (n = 141). Only 11 patients had

Crohn's disease (refer to section 3.3.2). Accordingly, most of the biologic immunomodulators claimed over the four years were claimed for patients with multiple sclerosis (60.39%) and patients with rheumatoid arthritis (37.73%), whereas the smallest percentage of biologic immunomodulators were claimed for Crohn's disease patients (1.88%) (refer to section 3.3.2).

From the analysis done in section 4.4 it was determined that biologic immunomodulators claimed for patients with multiple sclerosis indicated the beta interferons. Interferon beta-1a (Avonex® and Rebif®) represented almost two thirds of the total number of biologic immunomodulators claimed for multiple sclerosis patients during the study period, and interferon beta-1b (Betaferon®) represented the remaining third. This was in accord with the literature, as the literature stated that the beta interferons were the biologics indicated for treating multiple sclerosis (refer to section 4.4.2.2).

It was furthermore established that the biologic immunomodulators claimed for patients with rheumatoid arthritis were the TNF-alpha inhibitors, etanercept (Enbrel®), infliximab (Revellex®) and adalimumab (Humira®) (refer to section 4.4.1.2), but rituximab (MabThera®) (a B-lymphocyte depleting agent) was also claimed once for a patient with RA during the four years (refer to section 4.4.1.2). This was also consistent with the literature, since according to the literature the TNF-alpha inhibitors were the biologics of choice in the treatment of rheumatoid arthritis, whereas the use of rituximab to treat rheumatoid arthritis is still relatively recent (refer to section 4.4.1.2). The same three TNF-alpha inhibitors (adalimumab, etanercept and infliximab) were claimed for patients with Crohn's disease during the study period (refer to section 4.4.3.2), which was somewhat contradictory to the literature, because etanercept was claimed most frequently of all biologic immunomodulators for Crohn's disease patients, but according to South African literature (MIMS, SAMF) and the package insert of Enbrel®, it is not indicated for Crohn's disease.

According to the results, the prevalence of use of biologic immunomodulators for rheumatoid arthritis, multiple sclerosis and Crohn's disease in a section of the private health care sector of South Africa was lower than the use of these medicine items in the other diseases which they were indicated for. Out of the three diseases mostly patients with *multiple sclerosis* received biologic immunomodulators (i.e. beta interferons) in a section of the private health care sector of South Africa between 2005 and 2008, followed by patients with *rheumatoid arthritis* (i.e. TNF-alpha inhibitors).

- **Specific objective nine was to *determine the cost of biologic immunomodulators and how it compares to the cost of other medication (excluding biologics) received by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease.***

Overall, the results obtained from the data indicated that in general, biologic immunomodulators were relatively expensive (refer to discussion of specific objective six). From the data analysis it was determined that the biologic immunomodulators indicated to treat rheumatoid arthritis, multiple sclerosis or Crohn's disease and that were claimed through the PBM between 2005 and 2008 had average costs of between seven thousand and twelve thousand rand per medicine item, depending on the disease being treated (refer to sections 4.4.1.5, 4.4.2.5 and 4.4.3.5).

The average cost per biologic immunomodulator per patient was the highest for those biologics claimed for Crohn's disease (R10742.71 ± 11338.81). Biologics claimed for Crohn's disease patients represented ~0.00017% of the total number of medicine items claimed through the PBM during the four-year study period, whereas the cost of these medicine items represented ~0.01481% of the total medicine cost for that time (refer to sections 4.4.3.5 and 4.4.3.6). Biologic immunomodulators claimed for rheumatoid arthritis had an average cost of R8364.15 ± 1991.67 between 2005 and 2008, and represented ~0.00337% of the total number of medicine items and ~0.27671% of the total medicine cost of the total database (refer to sections 4.4.1.5 and 4.4.1.6). The biologic immunomodulators claimed for multiple sclerosis had the lowest average cost per patient (R7536.09 ± 743.56), and represented ~0.00539% of the total number of medicine items and ~0.41320% of the total medicine cost of the total database over the four-year study period (refer to sections 4.4.2.5 and 4.4.2.6).

The CPI of the biologic immunomodulators claimed for each of the respective autoimmune diseases *(CPI = 88.10 for Crohn's disease; CPI = 82.13 for rheumatoid arthritis and CPI = 76.61 for multiple sclerosis)* confirms that the biologic immunomodulators used in the treatment of these three autoimmune diseases are relatively expensive. It was thus established that the cost of biologic immunomodulators in a section of the private health care sector of South Africa was the highest for TNF-alpha inhibitors claimed for patients with *Crohn's disease,* followed by the TNF-alpha inhibitors claimed for patients with *rheumatoid arthritis*, whereas interferons (used to treat multiple sclerosis) had the lowest cost. Furthermore, it was determined that the average cost per biologic immunomodulator was practically significantly higher than the average cost per non-biological medicine item claimed for rheumatoid arthritis, multiple sclerosis or Crohn's disease. The *d*-values between the average cost per biological medicine item and the average cost of other medication

(excluding biologics) claimed for patients with rheumatoid arthritis (*d*-value = 4.1), multiple sclerosis (*d*-value = 9.9) or Crohn's disease (*d*-value = 0.9) indicate that the impact of biologic immunomodulators received by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease in a section of the private health care sector of South Africa between 2005 and 2008 was *large and practically significant*.

Accordingly, during the period when patients received biologic immunomodulators (phase two of treatment), the total medicine expenditure increased significantly from the period when they only received other medicine treatments (excluding biologics) (phase one). The total cost of medicine treatment during phase two of rheumatoid arthritis, multiple sclerosis and Crohn's disease treatment increased almost tenfold from what it had been prior to treatment with biologic immunomodulators. However, when treatment with biologic immunomodulators had stopped (phase three) the total cost of treatment once again decreased. The total cost of medicine treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease decreased with 126.90%, 116.49% and 112.02% respectively from before to after treatment with biologic immunomodulators (refer to sections 4.4.1.6, 4.4.2.6 and 4.4.3.6). The reason for the decrease in the total medicine treatment cost of these diseases could *inter alia* be ascribed to the fact that the number of medicine items and prescriptions claimed for patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease also decreased from before to after treatment (refer to sections 4.4.1.3, 4.4.2.3, 4.4.3.3 and discussion of specific objective ten). According to the data analysis it was established that treatment of rheumatoid arthritis, multiple sclerosis and Crohn's disease with biologic immunomodulators in a section of the private health care sector of South Africa between 2005 and 2008 was relatively expensive, but treatment with these agents seemed to decrease the total medicine treatment cost of other medication (excluding biologics), thus causing a decrease in the total medicine expenditure over time.

- **Specific objective ten was to *investigate the influence of biologic immunomodulators on the prescribing patterns of other medication (excluding biologics) after treatment with biologics in patients with rheumatoid arthritis, multiple sclerosis and Crohn's disease.***

On the whole, the results obtained from the study indicated that the total number of other medicine items and prescriptions (excluding biologics) claimed for patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease decreased from *before* to *after* treatment with biologic immunomodulators (refer to sections 4.4.1.3, 4.4.2.3 and 4.4.3.3). From the study

results, it thus seemed as though the utilisation of biologic immunomodulators by patients with rheumatoid arthritis, multiple sclerosis or Crohn's disease caused a decrease in the use of other medication by these patients.

However, clinical outcomes were not measured in this study, and patients were not monitored from before to after treatment with biologic immunomodulators. Therefore, the reason for the considerable decrease in the number of medicine items claimed for these patients through the PBM is difficult to explain. Furthermore, the composition of the prescriptions and the specific types of medicine items (other than biologics) claimed for the study population during the study period were not investigated. The decrease in the number of medicine items and prescriptions could, *inter alia,* be an indication that the use of biologic immunomodulators in rheumatoid arthritis, multiple sclerosis and Crohn's disease improves the disease outcome and reduces the need for other medication, changes in the type of medicine used by these patients, changes in prescription composition, patients leaving the medical aid scheme after treatment with biologics, patients' funds being exhausted after treatment with biologics and therefore not claiming any other medication for a while thereafter.

Conclusion

According to the results it is clear that biologics have led to dramatic change in the immunotherapy of autoimmune diseases. Biologics are currently only used by a small percentage of patients in a section of the private health care sector of South Africa, (below one per cent), but a single occurrence can be relatively expensive. It is evident that the cost burden associated with health care is being shifted from medical aid schemes to patients in response to accelerating health care costs, and that this has created access barriers to biological therapies, the cost burden of which can be sizeable. The potential benefits associated with these therapies, however, warrant examination in the context of health care coverage, financing, access and administration. The unintended consequences of limiting access and reimbursement for biologics could reverse well-meaning attempts to control and reduce total health care expenditures, since it seems that the utilisation of biologics does reduce total health care expenditure to those patients who used them. Even though biologic immunomodulators are stated to be effective, they are presently relatively expensive and for this reason cost is a significant consideration and careful patient and disease selection is crucial when medical aid schemes decide whether to provide and reimburse these products for their patients.

5.2 Recommendations

The researcher proposes the following recommendations from the analysed results and conclusions:

- More in-depth research should be conducted on the use of biologics in South Africa where clinical outcomes should be measured as to establish whether these products are cost-effective.
- The type of medication and the composition of the prescriptions claimed for patients during each phase of their treatment should be investigated. This would allow researchers to determine how not only the frequency, but also the *type* of medication changes from before to after treatment with biologics.
- Further research should be conducted on the duration of treatment with biologics and the compliance of patients with these medicine items.
- Further research could be done on other diseases for which biologic immunomodulators are indicated in South Africa.
- The MCC should compile a list of all the medicine items available in South Africa classified as “biologics” and include it as a pharmacological category in South African literature.

5.3 Limitations

Through the course of this study, there were several limiting factors that could have influenced the scope and applicability of the study. These limitations include the following:

- Literature on biologics (and especially their use in South Africa) was limited.
- Only one PBM’s data were used throughout the study, therefore no comparison was made regarding the prescribing patterns of biologics within the private health care sector of South Africa. Prescribing patterns of biologics in the public health care sector was also not investigated.

- No direct manipulation of the data was possible: all the data were analysed from the perspective that the information was reliable and valid from the PBM's database.

- External validity was limited, implying that the results can only be generalised to this specific database and study population.

- The lack of detailed clinical data (i.e. complete ICD-10 codes, diagnosis, medical history etc.) limited the application of the results to a certain extent.

- The analysis of data was limited to direct cost of medicine only. The biologic immunomodulators investigated in this study are injectable drugs that need to be administered by professional health workers. The cost of products such as cotton wool, alcohol swabs, needles, syringes and professional fees have not been included in the analysis of the data.

- Clinical outcomes were not measured in this study. This limited the application of pharmacoeconomic methods. A cost-effectiveness or cost-utilisation study would have provided a better indication of the effect of biological therapies, but was not possible because outcomes were unknown.

- There are no generics available for the biologic immunomodulators investigated in this research project and therefore a cost-minimalisation analysis was not possible.

5.4 Chapter summary

This chapter included the conclusions regarding the specific objectives that were set for this study and recommendations made for future studies. Factors that limited the scope of the study were also discussed.

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APPENDIX A

Therapeutic biological products

Appendix A: *List of products classified by the FDA's CDER as "therapeutic biologic products" (compiled from FDA, 2009b; Snyman, 2010)*

Active ingredient:	***Trade name in USA:***	***Trade name in South Africa (if available)****	***Indication for use:***
Abatacept	Orencia®	*Not available*	℘ Moderate to severe rheumatoid arthritis
Abciximab	ReoPro®	Reopro®	℘ Prevention of restenosis in patients undergoing coronary interventions (with anti platelet drugs and heparin) ℘ Treatment of a broader range of patients undergoing coronary intervention ℘ Treatment of patients with unstable angina not responding to conventional medical therapy when coronary intervention is planned within 24 hours
Adalimumab	Humira®	Humira®	℘ Moderately to severely active rheumatoid arthritis ℘ Can be used alone or in combination with methotrexate or other DMARDs
Agalsidase beta	Fabrazyme®	*Not available*	℘ Fabry disease
Aldesleukin	Proleukin®	*Not available*	℘ Metastatic melanoma
Alefacept	Amevive®	*Not available*	℘ Moderate to severe chronic plaque psoriasis
Alemtuzumab	Campath®	Mabcampath®	℘ B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and who have failed fludarabine therapy
Alglucosidase alfa	Myozyme®	*Not available*	℘ Enzyme replacement therapy (ERT) ℘ Orphan drug for treatment of Pompe disease
Alteplase	Activase®	*Not available*	℘ Restoration of function to central venous access devices
Anakinra	Kineret®	*Not available*	℘ Moderately to severely active rheumatoid arthritis in patients 18 years or older ℘ Still's disease ℘ Certain periodic fevers
Asparaginase	Elspar®	*Not available*	℘ Acute lymphocytic leukemia
Basilliximab	Simulect®	Simulect®	℘ Prevention of acute kidney rejection
Becaplermin	Regranex®	*Not available*	℘ Deep neuropathic diabetic foot ulcers
Bevacizumab	Avastin®	Avastin®	℘ Metastatic colorectal cancer (first-line treatment)

Botulinum Toxin A	Botox®	Botox®	℘ Cervical dystonia
Botulinum Toxin A	Botox cosmetic®	Botox®	℘ Temporary improvement in the appearance of moderate to severe glabellar lines in adult patients 65 years and older
Botulinum Toxin B	MYOBLOC®	*Not available*	℘ Cervical dystonia to reduce severity of abnormal head position and neck pain
Capromab Pendetide	ProstaScint®	*Not available*	℘ Locating and identifying previously diagnosed prostate cancer
Certolizumab pegol	Cimzia®	*Not available*	℘ Crohn's disease
Cetuximab	Erbitux®	Erbitux®	℘ Monoclonal antibody that targets a protein called epidermal growth factor receptor (EGFR)
Collagenase	Santyl®	Iruxol Mono®	℘ Helps healing of burns and skin ulcers
Daclizumab	Zenapax®	*Not available*	℘ Prevention of acute kidney rejection
Darbepoetin alfa	Aranesp®	*Not available*	℘ Anemia associated with chronic renal failure ℘ Anemia due to the effect of concomitantly administered chemotherapy in patients with non-myeloid malignancies
Denileukin diftitox	Ontak®	*Not available*	℘ Cutaneous T-cell lymphoma
Dornase alfa	Pulmozyme®	Pulmozyme®	℘ Cystic Fibrosis
Drotrecogin alfa	Xigris®	Xigris®	℘ Reduction of mortality in adult patients with severe sepsis who have a high risk of death
Eculizumab	Soliris®	*Not available*	℘ Reduction of hemolysis in paroxysmal nocturnal hemoglobinuria
Efalizumab	Raptiva®	*Not available*	℘ Psoriasis
Epoetin alfa	Epogen®	*Not available*	℘ Treatment of anemia in patients with chronic renal failure (CRF) on dialysis.
Etanercept	Enbrel®	Enbrel®	℘ Moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARD's) ℘ Polyarticular course juvenile rheumatoid arthritis (JRA) ℘ Reducing signs and symptoms of active arthritis in patients with psoriatic arthritis
Filgrastim	Neupogen®	Neupogen®	℘ Stimulates production of granulocytes in patients undergoing therapy that will cause low white blood cell counts ℘ Prevent infection and neutropenic (low white blood cells) fevers caused by chemotherapy
Galsulfase	Naglazyme®	*Not available*	℘ Mucopolysaccharidosis VI (MPS VI)

Ibritumomab tiuxetan	Zevalin®	Zevalin®	℘ Relapsed or refractory low-grade follicular or transformed B-cell non-Hodgkin lymphoma
Idursulfase	Elaprase®	*Not available*	Used to treat some of the symptoms of Hunter's syndrome.
Infliximab	Remicade®	Revellex®	℘ Moderate to severe Crohn's disease with or without fistulisation ℘ Moderate to severe rheumatoid arthritis inadequately responsive to methotrexate
Interferon alfa-2a	Roferon A®	Roferon A®	℘ Chronic hepatitis C ℘ Hairy cell leukemia ℘ AIDS-related Kaposi's sarcoma
Interferon alfa-2b	Intron A®	Intron A®	℘ Hepatitis B in pediatric patients ℘ Chronis hepatitis C ℘ Follicular lymphoma in conjunction with chemotherapy
Interferon alfacon-1	Infergen®	*Not available*	℘ Chronic hepatitis C virus in patients 18 years or older with compensated liver disease who have anti-HCV serum antibodies and/or presence of HCV RNA
Interferon alfa-n3	Alferon® N Injection	*Not available*	℘ Refractory or recurrent external condylomata acuminata (genital warts) in patients 18 years of age or older
Interferon beta-1a	Avonex®	Avonex®	℘ Multiple sclerosis (orphan indication)
Interferon beta-1a	Rebif®	Rebif®	℘ Multiple sclerosis (relapsing)
Interferon beta-1b	Betaseron®	Betaferon®	℘ Multiple sclerosis (relapsing)
Interferon gamma-1b	Actimmune®	*Not available*	℘ Severe, malignant osteoporosis
Laronidase	Aldurazyme®	*Not available*	℘ Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I)
Muromonab-CD3	Orthoclone OKT3®	*Not available*	℘ Acute treatment and prevention of heart, kidney, or liver transplant rejection
Natalizumab	Tysabri®	*Not available*	℘ Multiple sclerosis (relapsing) or Crohn's disease when other treatments are inadequate
Nofetumomab	Verluma®	*Not available*	℘ Detection of extensive stage disease in patients with biopsy-confirmed, previously untreated, small cell lung cancer
Omalizumab	Xolair®	*Not available*	℘ Moderate to severe asthma in patients > 12 years with documented allergic disorders inadequately controlled by inhaled corticosteroids
Oprelvekin	Neumega®	*Not available*	℘ Prevention of severe thrombocytopenia ℘ Reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of

			severe thrombocytopenia
Palifermin	Kepivance®	*Not available*	℘ Decreases the incidence and duration of severe oral mucositis in patients with hematological malignancies receiving myelotoxic therapy that requires hematopoietic stem cell support
Palivizumab	Synagis®	Synagis®	℘ Prophylaxis of serious lower respiratory tract disease by Respiratory Syncytial Virus in children at high risk of severe infections
Panitumumab	Vectibix®	*Not available*	℘ Metastatic colorectal cancer
Pegaspargase	Oncaspar®	*Not available*	℘ Acute lymphoblastic leukemia (ALL) ℘ ALL and hypersensitivity to native forms of L-asparaginase
Pegfilgrastim	Neulasta®	*Not available*	℘ Decreases the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Peginterferon alfa-2a	Pegasys®	Pegasys®	℘ Chronic hepatitis C in adults who have compensated liver disease and who have not been previously treated with interferon Alfa
Peginterferon alfa-2b	PegIntron®	PegIntron®	℘ Chronic hepatitis C in adult patients (at least 18 years) who have compensated liver disease and who have not been previously treated with interferon Alfa
Peginterferon alfa-2a and Ribavarin	Pegasys®/Copegus® Combination Pack	*Not available*	℘ Chronic hepatitis C virus infection in adult patients who have compensated liver disease and have not been previously treated with interferon Alpha
Peginterferon alfa-2b and Ribavarin	ReBETOL® Combo Pack	*Not available*	℘ Chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon Alpha, and who are at least 18 years old
Ranibizumab	Lucentis®	Lucentis®	℘ Neovascular age-related macular degeneration
Rasburicase	Elitek®	*Not available*	℘ Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid
Reteplase	Retavase®	*Not available*	℘ Acute myocardial infarction in adults
Rilonacept	Arcalyst®	*Not available*	℘ Cryopyrin-Associated Periodic Syndromes (CAPS), including ℘ Familial Cold Autoinflammatory Syndrome (FCAS) and ℘ Muckle-Wells Syndrome (MWS) in adults and children 12 and older
Rituximab	Rituxan®	MabThera®	℘ Relapsed or refractory low-grade or follicular B-cell non-Hodgkin lymphoma
Romiplostim	Nplate®	*Not available*	℘ Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids,

			immunoglobulins or splenectomy
Sargramostim	Leukine®	*Not available*	℘ Indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death
Tenecteplase	TKNase®	Metalyse®	℘ Reduction of mortality associated with acute myocardial infarction
Tositumomab and Iodine I-131 Tositumomab	Bexxar® Therapeutic Regime	*Not available*	℘ CD20 positive, follicular, non-Hodgki's lymphoma in patients whose disease is refractory to Rituximab and has relapsed following chemotherapy
Trastuzumab	Herceptin®	Herceptin®	℘ HER2-positive breast cancer
***According to Snyman 2010. If an active ingredient was not listed in the MIMS of January 2010, Vol. 50(1), it was regarded as not being available in South Africa**.			

APPENDIX B

Appendix tables

Table A.1 Average cost per medicine item for total database

AVERAGE COST PER MEDICINE ITEM FOR TOTAL DATABASE					
Year	**Variable**	**Frequency (n = medicine items)**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	Total cost	19,500,774	93.32 ± 166.36	1,819,865,251.63	100.00
	Scheme amount		82.17 ± 159.21	1,602,447,649.43	88.05
	Patient levy		11.15 ± 42.24	217,417,602.20	11.95
2006	Total cost	21,113,422	92.82 ± 196.42	1,959,738,734.09	100.00
	Scheme amount		80.46 ± 189.99	1,698,709,951.36	86.68
	Patient levy		12.36 ± 45.28	261,028,782.73	13.32
2007	Total cost	19,075,724	100.56 ± 324.11	1,918,284,176.66	100.00
	Scheme amount		84.66 ± 304.10	1,615,007,032.92	84.19
	Patient levy		15.90 ± 101.24	303,277,143.74	15.81
2008	Total cost	16,439,253	108.63 ± 436.75	1,785,871,013.85	100.00
	Scheme amount		89.94 ± 419.97	1,478,548,228.92	82.79
	Patient levy		18.69 ± 107.16	307,322,784.93	17.21

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.2 Average cost per medicine item for total database according to gender

AVERAGE COST PER MEDICINE ITEM ACCORDING TO GENDER FOR TOTAL DATABASE							
Year	**Gender**	**Variable**	**Frequency (n = medicine items)**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**F**	Total cost	11,750,190	60.25	92.31 ± 158.69	1084,626,865.29	100.00
		Scheme amount			80.65 ± 151.40	947,688,793.44	87.37
		Patient levy			11.65 ± 41.24	136,938,071.85	12.63
	M	Total cost	7,734,461	39.66	94.87 ± 176.88	733,769,633.85	100.00
		Scheme amount			84.48± 169.85	653,370,941.06	89.04
		Patient levy			10.39 ± 43.72	80,398,692.79	10.96
	U	Total cost	16,123	0.08	91.10 ± 329.67	1,468,752.49	100.00
		Scheme amount			86.08 ± 328.52	1,387,914.93	94.50
		Patient levy			5.01 ± 22.02	80,837.56	5.50
2006	**F**	Total cost	12,699,707	60.15	91.52 ± 188.12	1162,254,536.29	100.00
		Scheme amount			78.66 ± 181.38	999,015,475.00	85.95
		Patient levy			12.85 ± 45.46	163,239,061.29	14.05
	M	Total cost	8,403,158	39.80	94.77 ± 208.10	796,360,401.04	100.00
		Scheme amount			83.15 ± 202.04	698,682,181.29	87.73
		Patient levy			11.62 ± 45.01	97,678,219.75	12.27
	U	Total cost	10,557	0.05	106.45 ± 336.87	1,123,796.76	100.00
		Scheme amount			95.89 ± 335.07	1,012,295.07	90.08
		Patient levy			10.56 ± 33.12	111,501.69	9.92
2007	**F**	Total cost	11,509,346	60.34	98.89 ± 300.67	1138,188,990.86	100.00
		Scheme amount			82.46 ± 286.55	949,029,333.61	83.38
		Patient levy			16.44 ± 83.42	189,159,657.25	16.62
	M	Total cost	7,562,466	39.64	103.08 ± 356.74	779,508,488.81	100.00
		Scheme amount			88.00 ± 328.91	665,466,500.10	85.37
		Patient levy			15.08 ± 123.54	114,041,988.71	14.63
	U	Total cost	3,912	0.02	149.97 ± 445.38	586,696.99	100.00
		Scheme amount			130.67 ± 443.53	511,199.21	87.13
		Patient levy			19.30 ± 28.79	75,497.78	12.87
2008	**F**	Total cost	9,893,928	60.18	106.86 ± 416.84	1057,274,453.63	100.00
		Scheme amount			87.52 ± 397.36	865,959,792.23	81.90
		Patient levy			19.34 ± 116.02	191,314,661.40	18.10
	M	Total cost	6,545,325	39.82	111.32 ± 465.21	728,596,560.22	100.00
		Scheme amount			93.59 ± 451.99	612,588,436.69	84.08
		Patient levy			17.72 ± 92.16	116,008,123.53	15.92
	U	Total cost	0	0	-	-	-
		Scheme amount			-	-	-
		Patient levy			-	-	-

F = Female; M = Male; U = Unidentified.

% items = percentage of total number of medicine items on database claimed by each gender.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.3 Average cost per medicine item for total database according to age

AVERAGE COST PER MEDICINE ITEM ACCORDING TO AGE FOR TOTAL DATABASE							
Year	**Age group**	**Variable**	**Frequency (n = medicine items)**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**1**	Total cost	3,658,580	18.76	65.54 ± 101.13	239,766,846.41	100.00
		Scheme amount			58.74 ± 95.32	214,897,939.98	89.63
		Patient levy			6.80 ± 29.14	24,868,906.43	10.37
	2	Total cost	2,930,322	15.03	77.40 ± 148.62	226,818,610.94	100.00
		Scheme amount			70.12 ± 142.95	205,479,491.44	90.59
		Patient levy			7.28 ± 36.32	21,339,119.50	9.41
	3	Total cost	8,363,409	42.89	97.08 ± 176.48	811,952,830.36	100.00
		Scheme amount			86.21 ± 169.38	721,025,658.60	88.80
		Patient levy			10.87 ± 45.59	90,927,171.76	11.20
	4	Total cost	4,548,463	23.32	119.01 ± 193.54	541,326,963.92	100.00
		Scheme amount			101.36 ± 185.77	461,044,559.41	85.17
		Patient levy			17.65 ± 47.19	80,282,404.51	14.83
2006	**1**	Total cost	3,912,699	18.53	64.95 ± 113.93	254,141,563.62	100.00
		Scheme amount			56.77 ± 107.71	222,111,395.73	87.40
		Patient levy			8.19 ± 33.36	32,030,167.89	12.60
	2	Total cost	3,068,900	14.54	76.47 ± 169.84	234,674,113.15	100.00
		Scheme amount			67.96 ± 163.44	208,554,713.53	88.87
		Patient levy			8.51 ± 41.72	26,119,399.62	11.13
	3	Total cost	9,261,669	43.87	96.15 ± 209.04	890,470,151.20	100.00
		Scheme amount			84.33 ± 203.00	781,008,788.47	87.71
		Patient levy			11.82 ± 46.52	109,461,362.73	12.29
	4	Total cost	4,870,154	23.07	119.19 ± 232.49	580,452,906.12	100.00
		Scheme amount			100.00 ± 225.84	487,035,053.63	83.91
		Patient levy			19.18 ± 52.07	93,417,852.49	16.09
2007	**1**	Total cost	3,346,576	17.54	68.42 ± 163.51	228,982,535.62	100.00
		Scheme amount			57.11 ± 146.54	191,117,985.47	83.46
		Patient levy			11.31 ± 66.36	37,864,550.15	16.54
	2	Total cost	2,528,016	13.25	81.77 ± 263.69	206,723,414.80	100.00
		Scheme amount			69.79 ± 252.80	176,421,796.24	85.34
		Patient levy			11.99 ± 66.83	30,301,618.56	14.66
	3	Total cost	8,494,142	44.53	103.40 ± 353.70	878,327,951.34	100.00
		Scheme amount			88.40 ± 334.16	750,921,044.36	85.49
		Patient levy			15.00 ± 101.86	127,406,906.98	14.51
	4	Total cost	4,706,990	24.68	128.37 ± 376.68	604,250,274.90	100.00
		Scheme amount			105.49 ± 350.11	496,546,206.85	82.18
		Patient levy			22.88 ± 131.19	107,704,068.05	17.82
2008	**1**	Total cost	2,421,518	14.73	75.49 ± 210.85	182,794,294.08	100.00
		Scheme amount			61.95 ± 201.09	150,022,179.26	82.07
		Patient levy			13.53 ± 51.49	32,772,114.82	17.93
	2	Total cost	1,876,874	11.42	90.16 ± 363.99	169,227,300.16	100.00
		Scheme amount			75.70 ± 345.02	142,085,583.63	83.96
		Patient levy			14.46 ± 97.47	27,141,716.53	16.04

	3	Total cost	7,639,419	46.47	109.54 ± 466.22	836,842,632.27	100.00
		Scheme amount			92.09 ± 450.59	703,481,122.70	84.06
		Patient levy			17.46 ± 109.70	133,361,509.57	15.94
	4	Total cost	4,501,442	27.38	132.63 ± 497.24	597,006,787.34	100.00
		Scheme amount			107.29 ± 476.82	482,959,343.33	80.90
		Patient levy			25.34 ± 126.73	114,047,444.01	19.10

Age group 1 = < 25 years; Age group 2 = 25-39 years; Age group 3 = 40-64 years; Age group 4 = ≥ 65 years.

% items = percentage of total number of medicine items on database claimed by each age group.

SD = Standard Deviation.

% = percentage contribution of the medical aid scheme and the patient to the final cost.

Table A.4 Average cost per prescription for total database

AVERAGE COST PER PRESCRIPTION FOR TOTAL DATABASE					
Year	**Variable**	**Frequency (n = prescriptions)**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	Total cost	8,391,836	216.86 ± 342.30	1,819,865,251.63	100.00
	Scheme amount		190.95 ± 323.66	1,602,447,649.43	88.05
	Patient levy		25.91 ± 81.07	217,417,602.20	11.95
2006	Total cost	8,906,348	220.04 ± 395.22	1,959,738,734.09	100.00
	Scheme amount		190.73 ± 377.73	1,698,709,951.36	86.68
	Patient levy		29.31 ± 88.47	261,028,782.73	13.32
2007	Total cost	7,911,096	242.48 ± 600.31	1,918,284,176.66	100.00
	Scheme amount		204.14 ± 564.37	1,615,007,032.92	84.19
	Patient levy		38.34 ± 171.45	303,277,143.74	15.81
2008	Total cost	6,775,873	263.56 ± 789.01	1,785,871,013.85	100.00
	Scheme amount		218.21 ± 756.95	1,478,548,228.92	82.79
	Patient levy		45.36 ± 181.31	307,322,784.93	17.21

SD = Standard Deviation.

% = percentage contribution of the medical aid and the patient to the final cost.

Table A.5 Average cost per prescription for total database according to gender

AVERAGE COST PER PRESCRIPTION ACCORDING TO GENDER FOR TOTAL DATABASE							
Year	**Gender**	**Variable**	**Frequency (n = prescriptions)**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**F**	Total cost	5,036,494	60.12	215.35 ± 330.75	1,084,626,865.29	100.00
		Scheme amount			188.16 ± 310.90	947,688,793.44	87.37
		Patient levy			27.19 ± 80.87	136,938,071.85	12.63
	M	Total cost	3,348,219	39.90	219.15 ± 358.17	733,769,633.85	100.00
		Scheme amount			195.14 ± 341.05	653,370,941.06	89.04
		Patient levy			24.01 ± 81.38	80,398,692.79	10.96
	U	Total cost	7,123	0.08	206.20 ± 622.31	1,468,752.49	100.00
		Scheme amount			194.85 ± 615.57	1,387,914.93	94.50
		Patient levy			11.35 ± 41.06	80,837.56	5.50
2006	**F**	Total cost	5,336,203	59.91	217.81 ± 380.43	1162,254,536.29	100.00
		Scheme amount			187.21 ± 361.56	999,015,475.00	85.95
		Patient levy			30.59 ± 89.95	163,239,061.29	14.05
	M	Total cost	3,565,331	40.03	223.36 ± 416.16	796,360,401.04	100.00
		Scheme amount			195.97 ± 400.43	698,682,181.29	87.73
		Patient levy			27.40 ± 86.20	97,678,219.75	12.27
	U	Total cost	4,814	0.05	233.44 ± 529.46	1,123,796.76	100.00
		Scheme amount			210.28 ± 524.10	1,012,295.07	90.08
		Patient levy			23.16 ± 59.04	111,501.69	9.92
2007	**F**	Total cost	4,754,911	60.10	239.37 ± 559.98	1138,188,990.86	100.00
		Scheme amount			199.59 ± 530.41	949,029,333.61	83.38
		Patient levy			39.78 ± 148.33	189,159,657.25	16.62
	M	Total cost	3,154,367	39.87	247.12 ± 656.34	779,508,488.81	100.00
		Scheme amount			210.97 ± 611.87	665,466,500.10	85.37
		Patient levy			36.15 ± 201.38	114,041,988.71	14.63
	U	Total cost	1,818	0.02	322.72 ± 697.81	586,696.99	100.00
		Scheme amount			281.19 ± 688.75	511,199.21	87.13
		Patient levy			41.53 ± 53.27	75,497.78	12.87
2008	**F**	Total cost	4,062,385	59.95	260.26 ± 752.96	1057,274,453.63	100.00
		Scheme amount			213.17 ± 716.56	865,959,792.23	81.90
		Patient levy			47.09 ± 195.17	191,314,661.40	18.10
	M	Total cost	2,713,488	40.05	268.51 ± 840.07	728,596,560.22	100.00
		Scheme amount			225.76 ± 813.62	612,588,436.69	84.08
		Patient levy			42.75 ± 158.27	116,008,123.53	15.92
	U	Total cost	0	0	-	-	-
		Scheme amount			-	-	-
		Patient levy			-	-	-

F = Female; M = Male; U = Unidentified.

% Rx = percentage of total number of prescriptions on database claimed each gender.

% = percentage contribution of the medical aid scheme and the patient to the final cost.

Table A.6 Average cost per prescription for total database according to age

AVERAGE COST PER PRESCRIPTION ACCORDING TO AGE FOR TOTAL DATABASE							
Year	**Age group**	**Variable**	**Frequency (n = prescriptions)**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**1**	Total cost	1,552,841	18.50	154.41 ± 190.13	239,766,846.41	100.00
		Scheme amount			138.39 ± 179.38	214,897,939.98	89.63
		Patient levy			16.02 ± 53.97	24,868,906.43	10.37
	2	Total cost	1,319,940	15.73	171.84 ± 289.74	226,818,610.94	100.00
		Scheme amount			155.67 ± 278.26	205,479,491.44	90.59
		Patient levy			16.17 ± 66.25	21,339,119.50	9.41
	3	Total cost	3,669,930	43.73	221.24 ± 358.41	811,952,830.36	100.00
		Scheme amount			196.47 ± 341.04	721,025,658.60	88.80
		Patient levy			24.78 ± 84.72	90,927,171.76	11.20
	4	Total cost	1,849,125	22.03	292.75 ± 419.52	541,326,963.92	100.00
		Scheme amount			249.33 ± 394.46	461,044,559.41	85.17
		Patient levy			43.42 ± 97.67	80,282,404.51	14.83
2006	**1**	Total cost	1,633,373	18.34	155.59 ± 213.41	254,141,563.62	100.00
		Scheme amount			135.98 ± 201.78	222,111,395.73	87.40
		Patient levy			19.61 ± 63.22	32,030,167.89	12.60
	2	Total cost	1,367,117	15.35	171.66 ± 315.33	234,674,113.15	100.00
		Scheme amount			152.55 ± 302.11	208,554,713.53	88.87
		Patient levy			19.11 ± 74.62	26,119,399.62	11.13
	3	Total cost	3,968,128	44.55	224.41 ± 416.63	890,470,151.20	100.00
		Scheme amount			196.82 ± 400.70	781,008,788.47	87.71
		Patient levy			27.59 ± 89.14	109,461,362.73	12.29
	4	Total cost	1,937,730	21.76	299.55 ± 492.37	580,452,906.12	100.00
		Scheme amount			251.34 ± 470.10	487,035,053.63	83.91
		Patient levy			48.21 ± 109.03	93,417,852.49	16.09
2007	**1**	Total cost	1,397,144	5.02	163.89 ± 292.33	228,982,535.62	100.00
		Scheme amount			136.79 ± 259.00	191,117,985.47	83.46
		Patient levy			27.10 ± 122.80	37,864,550.15	16.54
	2	Total cost	1,112,243	14.06	185.86 ± 470.34	206,723,414.80	100.00
		Scheme amount			158.62 ± 449.21	176,421,796.24	85.34
		Patient levy			27.24 ± 115.07	30,301,618.56	14.66
	3	Total cost	3,563,317	45.04	246.49 ± 649.89	878,327,951.34	100.00
		Scheme amount			210.74 ± 616.78	750,921,044.36	85.49
		Patient levy			35.76 ± 167.99	127,406,906.98	14.51
	4	Total cost	1,838,392	23.24	328.68 ± 720.57	604,250,274.90	100.00
		Scheme amount			270.10 ± 671.64	496,546,206.85	82.18
		Patient levy			58.59 ± 227.46	107,704,068.05	17.82
2008	**1**	Total cost	1,034,765	15.27	176.65 ± 365.21	182,794,294.08	100.00
		Scheme amount			144.98 ± 345.12	150,022,179.26	82.07
		Patient levy			31.67 ± 90.49	32,772,114.82	17.93
	2	Total cost	836,129	12.34	202.39 ± 631.89	169,227,300.16	100.00
		Scheme amount			169.93 ± 597.93	142,085,583.63	83.96
		Patient levy			32.46 ± 159.88	27,141,716.53	16.04

	3	Total cost	3,172,135	46.82	263.81 ± 839.12	836,842,632.27	100.00
		Scheme amount			221.77 ± 810.00	703,481,122.70	84.06
		Patient levy			42.04 ± 182.14	133,361,509.57	15.94
	4	Total cost	1,732,844	25.57	344.52 ± 927.44	597,006,787.34	100.00
		Scheme amount			278.71 ± 887.57	482,959,343.33	80.90
		Patient levy			65.82 ± 223.52	114,047,444.01	19.10

Age group 1 = < 25 years; Age group 2 = 25-39 years; Age group 3 = 40-64 years; Age group 4 = ≥ 65 years.

% Rx = percentage prescriptions of total number of prescriptions claimed by each age group.

% = percentage contribution of the medical aid scheme and the patient to the final cost.

Table A.7 Average number of medicine items per prescription for total database

AVERAGE NUMBER OF MEDICIEN ITEMS PER PRESCRIPTION FOR TOTAL DATABASE			
Year	**Total number of prescriptions**	**Total number of medicine items**	**Average number of medicine items per Rx Mean ± SD**
2005	8,391,836	19,500,774	2.32 ± 1.52
2006	8,906,348	21,113,422	2.37 ± 1.55
2007	7,911,096	19,075,724	2.41 ± 1.59
2008	6,775,873	16,439,253	2.43 ± 1.64

SD = standard deviation.

Table A.8 Average number of medicine items per prescription for total database according to gender

AVERAGE NUMBER OF MEDICIEN ITEMS PER PRESCRIPTION FOR TOTAL DATABASE				
Year	**Gender**	**Total number of prescriptions**	**Total number of medicine items**	**Average number of medicine items per Rx Mean ± SD**
2005	**F**	5,036,494	11,750,190	2.33 ± 1.54
	M	3,348,219	7,734,461	2.31 ± 1.47
	U	7,123	16,123	2.26 ± 1.37
2006	**F**	5,336,203	12,699,707	2.38 ± 1.58
	M	3,565,331	8,403,158	2.36 ± 1.50
	U	4,814	10,557	2.19 ± 1.41
2007	**F**	4,754,911	11,509,346	2.42 ± 1.62
	M	3154367	7,562,466	2.40 ± 1.55
	U	1818	3,912	2.15 ± 1.47
2008	**F**	4,062,385	9,893,928	2.44 ± 1.67
	M	2,713,488	6,545,325	2.41 ± 1.59

F = Female; M = Male; U = Unidentified.

Table A.9 Average number of medicine items per prescription for total database according to age

AVERAGE NUMBER OF MEDICIEN ITEMS PER PRESCRIPTION FOR TOTAL DATABASE				
Year	**Age group**	**Total number of prescriptions**	**Total number of medicine items**	**Average number of medicine items per Rx Mean ± SD**
2005	**1**	1,552,841	3,658,580	2.36 ± 1.33
	2	1,319,940	2,930,322	2.22 ± 1.33
	3	3,669,930	8,363,409	2.28 ± 1.48
	4	1,849,125	4,548,463	2.46 ± 1.82
2006	**1**	1,633,373	3,912,699	2.40 ± 1.35
	2	1,367,117	3,068,900	2.24 ± 1.35
	3	3,968,128	9,261,669	2.33 ± 1.51
	4	1,937,730	4,870,154	2.51 ± 1.87
2007	**1**	1,397,144	3,346,576	2.40 ± 1.36
	2	1,112,243	2,528,016	2.27 ± 1.37
	3	3,563,317	8,494,142	2.38 ± 1.56
	4	1,838,392	4,706,990	2.56 ± 1.91
2008	**1**	1,034,765	2,421,518	2.34 ± 1.36
	2	836,129	1,876,874	2.24 ± 1.37
	3	3,172,135	7,639,419	2.41 ± 1.59
	4	1,732,844	4,501,442	2.60 ± 1.95
Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years. **SD = Standard Deviation.**				

Table A.10 Average number of prescriptions per patient for total database

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT FOR TOTAL DATABASE			
Year	**Total number of patients**	**Total number of prescriptions**	**Average number of prescriptions per patient Mean ± SD**
2005	1,509,621	8,391,836	5.56 ± 6.75
2006	1,558,090	8,906,344	5.72 ± 6.96
2007	1,178,596	7,911,084	6.71 ± 7.55
2008	974,497	6,775,863	6.95 ± 7.85
SD = Standard Deviation.			

Table A.11 Average number of prescriptions per patient for total database according to gender

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT FOR TOTAL DATABASE				
Year	**Gender**	**Total number of patients**	**Total number of prescriptions**	**Average number of prescriptions per patient Mean ± SD**
2005	**F**	842,386	5,036,494	5.98 ± 7.16
	M	665,505	3,348,219	5.03 ± 6.15
	U	1,730	7,123	4.12 ± 5.21
2006	**F**	868,891	5,336,202	6.14 ± 7.37
	M	688,091	3,565,328	5.18 ± 6.35
	U	1,108	4,814	4.34 ± 5.78
2007	**F**	654,348	4,754,911	7.27 ± 7.99
	M	523,841	3,154,355	6.02 ± 6.90
	U	407	1,818	4.47 ± 5.20
2008	**F**	538,254	4,062,385	7.55 ± 8.32
	M	436,243	2,713,478	6.22 ± 7.15
	U	-	-	-
F = Female; M = Male; U = Unidentified.				

Table A.12 Average number of prescriptions per patient for total database according to age

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT FOR TOTAL DATABASE				
Year	**Age group**	**Total number of patients**	**Total number of prescriptions**	**Average number of prescriptions per patient Mean ± SD**
2005	**1**	493,907	1,552,841	3.14 ± 3.32
	2	291,872	1,319,940	4.52 ± 5.09
	3	556,022	3,669,930	6.60 ± 7.29
	4	167,820	1,849,125	11.02 ± 10.19
2006	**1**	499,442	1,633,373	3.27 ± 3.46
	2	300,056	1367,114	4.56 ± 5.25
	3	588,107	3,968,127	6.75 ± 7.46
	4	170,485	1,937,730	11.37 ± 10.54
2007	**1**	394,672	1,397,144	3.54 ± 3.68
	2	202,901	1,112,243	5.48 ± 5.74
	3	447,503	3,563,317	7.96 ± 7.94
	4	133,520	1,838,380	13.77 ± 10.72
2008	**1**	293,599	1,034,765	3.52 ± 3.78
	2	152,974	836,129	5.37 ± 5.89
	3	400,575	3,172,125	7.92 ± 7.97
	4	127,349	1,732,844	13.61 ± 10.93
Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years. **SD = Standard Deviation.**				

Table A.13 Frequency and cost of biologic immunomodulators

AVERAGE COST PER MEDICINE ITEM					
Year	**Variable**	**Number of medicine items**	**Mean ± SD**	**Total cost (R)**	**%**
2005	Total cost	1,759	5602.71 ± 2166.61	9,855,161.01	100.00
	Scheme amount		5398.44 ± 2299.56	9,495,851.34	96.35
	Patient levy		204.27 ± 1050.60	359,309.67	3.65
2006	Total cost	2,829	6698.90 ± 1990.97	18,951,176.69	100.00
	Scheme amount		6560.42 ± 2125.64	18,559,432.28	97.93
	Patient levy		138.47 ± 866.29	391,744.41	2.07
2007	Total cost	3,595	8633.78 ± 3821.67	31,038,438.00	100.00
	Scheme amount		8400.62 ± 3998.51	30,200,226.57	97.30
	Patient levy		233.16 ± 1411.16	838,211.43	2.70
2008	Total cost	3,731	9586.25 ± 5956.56	35,766,286.42	100.00
	Scheme amount		9400.26 ± 6052.02	35,072,366.57	98.06
	Patient levy		185.99 ± 1218.94	693,919.85	1.94
AVERAGE COST PER PRESCRIPTION					
Year	**Variable**	**Number of prescriptions**	**Mean ± SD**	**Total cost (R)**	**%**
2005	Total cost	1,319	7471.69 ± 4489.77	9,855,161.01	100.00
	Scheme amount		7199.28 ± 4604.33	9,495,851.34	96.35
	Patient levy		272.41 ± 1251.63	359,309.67	3.65
2006	Total cost	2,054	9226.47 ± 4959.61	18,951,176.69	100.00
	Scheme amount		9035.75 ± 5093.86	18,559,432.28	97.93
	Patient levy		190.72 ± 1053.75	391,744.41	2.07
2007	Total cost	2,971	10447.13 ± 6337.29	31,038,438.00	100.00
	Scheme amount		10165.00 ± 6457.94	30,200,226.57	97.30
	Patient levy		282.13 ± 1734.71	838,211.43	2.70
2008	Total cost	3,193	11201.47 ± 8890.93	35,766,286.42	100.00
	Scheme amount		10984.14 ± 8936.03	35,072,366.57	98.06
	Patient levy		217.33 ± 1424.89	693,919.85	1.94

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION			
Year	**Total number of prescriptions**	**Average items per Rx Mean ± SD**	**Total number of medicine items**
2005	1,319	1.33 ± 0.78	1,759
2006	2,054	1.38 ± 0.83	2,829
2007	2,971	1.21 ± 0.49	3,595
2008	3,193	1.17 ± 0.41	3,731

AVERAGE NUMBER OF PRESCRIPTIONS PER PATIENT			
Year	**Total number of patients**	**Average Rx per patient Mean ± SD**	**Total number of prescriptions**
2005	198	6.66 ± 5.00	1,319
2006	279	7.36 ± 4.50	2,054
2007	372	7.99 ± 4.49	2,971
2008	416	7.68 ± 4.77	3,193

Table A.14 Frequency and cost of biologic immunomodulators according to females

AVERAGE COST PER MEDICINE ITEM							
Year	**Gender**	**Variable**	**Number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**F**	Total cost	1,198	68.11	5589.80 ± 2172.58	6,696,578.10	100.00
		Scheme amount			5391.17 ± 2276.93	6,458,625.72	96.45
		Patient levy			198.62 ± 1006.86	237,952.38	3.55
2006	**F**	Total cost	1,851	65.43	6706.04 ± 1955.44	12,412,874.96	100.00
		Scheme amount			6536.76 ± 2102.68	12,099,541.59	97.48
		Patient levy			169.28 ± 933.54	313,333.37	2.52
2007	**F**	Total cost	2,292	63.76	8338.12 ± 3733.62	19,110,975.64	100.00
		Scheme amount			8141.45 ± 3863.62	18,660,195.15	97.64
		Patient levy			196.68 ± 1255.12	450,780.49	2.36
2008	**F**	Total cost	2,386	63.95	9113.39 ± 5031.73	21,744,544.89	100.00
		Scheme amount			8937.18 ± 5141.86	21,324,107.35	98.07
		Patient levy			176.21 ± 1147.06	420,437.54	1.93
AVERAGE COST PER PRESCRIPTION							
Year	**Gender**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**F**	Total cost	950	72.02	7049.03 ± 3817.07	6,696,578.10	100.00
		Scheme amount			6798.55 ± 3979.38	6,458,625.72	96.45
		Patient levy			250.48 ± 1125.06	237,952.38	3.55
2006	**F**	Total cost	1,479	72.00	8392.75 ± 3497.26	12,412,874.96	100.00
		Scheme amount			8180.89 ± 3658.27	12,099,541.59	97.48
		Patient levy			211.85 ± 1066.59	313,333.37	2.52
2007	**F**	Total cost	2,008	67.58	9517.42 ± 5415.84	19,110,975.64	100.00
		Scheme amount			9292.93 ± 5478.63	18,660,195.15	97.64
		Patient levy			224.49 ± 1499.42	450,780.49	2.36
2008	**F**	Total cost	2,133	66.80	10194.35 ± 7836.56	21,744,544.89	100.00
		Scheme amount			9997.24 ± 7895.03	21,324,107.35	98.07
		Patient levy			197.11 ± 1257.95	420,437.54	1.93
AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION							
Year		**Gender**	**Total number of Rx**		**Mean ± SD (Items)**	**Total number of medicine items**	
2005		**F**	950		1.26 ± 0.70	1,198.00	
2006		**F**	1,479		1.25 ± 0.64	1,851.00	
2007		**F**	2,008		1.14 ± 0.41	2,292.00	
2008		**F**	2,133		1.12 ± 0.34	2,386.00	

Table A.15 Frequency and cost of biologic immunomodulators according to males

AVERAGE COST PER MEDICINE ITEM							
Year	**Gender**	**Variable**	**Total number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**M**	Total cost	561	31.89	5630.27 ± 2155.47	3,158,582.91	100.00
		Scheme amount			5413.95 ± 2349.15	3,037,225.62	96.16
		Patient levy			216.32 ± 1139.24	121,357.29	3.84
2006	**M**	Total cost	978	34.57	6685.38 ± 2057.49	6,538,301.73	100.00
		Scheme amount			6605.21 ± 2168.80	6,459,890.69	98.80
		Patient levy			80.17 ± 718.92	78,411.04	1.20
2007	**M**	Total cost	1,303	36.24	9153.85 ± 3919.50	11,927,462.36	100.00
		Scheme amount			8856.51 ± 4188.10	11,540,031.42	96.75
		Patient levy			297.34 ± 1648.78	387,430.94	3.25
2008	**M**	Total cost	1,345	36.05	10425.09 ± 7241.51	14,021,741.53	100.00
		Scheme amount			10221.75 ± 7326.50	13,748,259.22	98.05
		Patient levy			203.33 ± 1337.26	273,482.31	1.95
AVERAGE COST PER PRESCRIPTION							
Year	**Gender**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	
2005	**M**	Total cost	369	27.98	8559.85 ± 5742.37	3,158,582.91	100.00
		Scheme amount			8230.96 ± 5797.35	3,037,225.62	96.16
		Patient levy			328.88 ± 1530.42	121,357.29	3.84
2006	**M**	Total cost	575	27.99	11370.96 ± 7077.18	6,538,301.73	100.00
		Scheme amount			11234.59 ± 7184.61	6,459,890.69	98.80
		Patient levy			136.37 ± 1018.87	78,411.04	1.20
2007	**M**	Total cost	963	32.41	12385.73 ± 7565.11	11,927,462.36	100.00
		Scheme amount			11983.42 ± 7825.49	11,540,031.42	96.75
		Patient levy			402.32 ± 2139.73	387,430.94	3.25
2008	**M**	Total cost	1,060	33.20	13228.06 ± 10415.18	14,021,741.53	100.00
		Scheme amount			12970.06 ± 10454.30	13,748,259.22	98.05
		Patient levy			258.00 ± 1712.14	273,482.31	1.95

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Gender**	**Total number of prescriptions**	**Average items per Rx Mean ± SD**	**Total number of medicine items**
2005	**M**	369	1.52 ± 0.95	561.00
2006	**M**	575	1.70 ± 1.12	978.00
2007	**M**	963	1.35 ± 0.60	1,303.00
2008	**M**	1,060	1.27 ± 0.50	1,345.00

Table A.16 Average cost per medicine item according to gender: total database vs target population

AVERAGE COST PER ITEM ACCORDING TO GENDER FOR TOTAL DATABASE						AVERAGE COST PER ITEM ACCORDING TO GENDER FOR BIOLOGIC IMMUNOMODULATORS							
Year	Gender	Variable	Frequency (n)	Mean ± SD (R)	Total cost (R)	Year	Gender	Variable	Frequency (n)	% n	Mean ± SD (R)	Total cost (R)	% R
2005	F	Total cost	11,750,190	92.31 ± 158.69	1084,626,865.29	2005	F	Total cost	1,198	0.010	5589.80 ± 2172.58	669,6578.10	0.62
		Scheme amount		80.65 ± 151.40	947,688,793.44			Scheme amount			5391.17 ± 2276.93	6,458,625.72	
		Patient levy		11.65 ± 41.24	136,938,071.85			Patient levy			198.62 ± 1006.86	237,952.38	
	M	Total cost	7,734,461	94.87 ± 176.88	733,769,633.85		M	Total cost	561	0.007	5630.27 ± 2155.47	3,158,582.91	0.43
		Scheme amount		84.48± 169.85	653,370,941.06			Scheme amount			5413.95 ± 2349.15	3,037,225.62	
		Patient levy		10.39 ± 43.72	80,398,692.79			Patient levy			216.32 ± 1139.24	121,357.29	
	U	Total cost	16,123	91.10 ± 329.67	1,468,752.49		U	Total cost	0	0	-	0.00	0
		Scheme amount		86.08 ± 328.52	1,387,914.93			Scheme amount			-	0.00	
		Patient levy		5.01 ± 22.02	80,837.56			Patient levy			-	0.00	
2006	F	Total cost	12,699,707	91.52 ± 188.12	1162,254,536.29	2006	F	Total cost	1,851	0.015	6706.04 ± 1955.44	12,412,874.96	1.07
		Scheme amount		78.66 ± 181.38	999,015,475.00			Scheme amount			6536.76 ± 2102.68	12,099,541.59	
		Patient levy		12.85 ± 45.46	163,239,061.29			Patient levy			169.28 ± 933.54	313,333.37	
	M	Total cost	8,403,158	94.77 ± 208.10	796,360,401.04		M	Total cost	978	0.012	6685.38 ± 2057.49	6,538,301.73	0.82
		Scheme amount		83.15 ± 202.04	698,682,181.29			Scheme amount			6605.21 ± 2168.80	6,459,890.69	
		Patient levy		11.62 ± 45.01	97,678,219.75			Patient levy			80.17 ± 718.92	78,411.04	
	U	Total cost	10,557	106.45 ± 336.87	1,123,796.76		U	Total cost	0	0	-	0.00	0
		Scheme amount		95.89 ± 335.07	1,012,295.07			Scheme amount			-	0.00	
		Patient levy		10.56 ± 33.12	111,501.69			Patient levy			-	0.00	
2007	F	Total cost	11,509,346	98.89 ± 300.67	1138,188,990.86	2007	F	Total cost	2,292	0.020	8338.12 ± 3733.62	19,110,975.64	1.68
		Scheme amount		82.46 ± 286.55	949,029,333.61			Scheme amount			8141.45 ± 3863.62	18,660,195.15	
		Patient levy		16.44 ± 83.42	189,159,657.25			Patient levy			196.68 ± 1255.12	450,780.49	
	M	Total cost	7,562,466	103.08 ± 356.74	779,508,488.81		M	Total cost	1,303	0.017	9153.85 ± 3919.50	11,927,462.36	1.53
		Scheme amount		88.00 ± 328.91	665,466,500.10			Scheme amount			8856.51 ± 4188.10	11,540,031.42	
		Patient levy		15.08 ± 123.54	114,041,988.71			Patient levy			297.34 ± 1648.78	387,430.94	

	U	Total cost	3,912	149.97 ± 445.38	586,696.99		**U**	Total cost	0	0	-	0.00	0
		Scheme amount		130.67 ± 443.53	511,199.21			Scheme amount			-	0.00	
		Patient levy		19.30 ± 28.79	75,497.78			Patient levy			-	0.00	
2008	**F**	Total cost	9,893,928	106.86 ± 416.84	1057,274,453.63	***2008***	**F**	Total cost	2,386	0.024	9113.39 ± 5031.73	21,744,544.89	2.06
		Scheme amount		87.52 ± 397.36	865,959,792.23			Scheme amount			8937.18 ± 5141.86	21,324,107.35	
		Patient levy		19.34 ± 116.02	191,314,661.40			Patient levy			176.21 ± 1147.06	420,437.54	
	M	Total cost	6,545,325	111.32 ± 465.21	728,596,560.22		**M**	Total cost	1,345	0.021	10425.09 ± 7241.51	1,4021,741.53	1.92
		Scheme amount		93.59 ± 451.99	612,588,436.69			Scheme amount			10221.75 ± 7326.50	13,748,259.22	
		Patient levy		17.72 ± 92.16	116,008,123.53			Patient levy			203.33 ± 1337.26	273,482.31	
	U	Total cost	0	-	-		**U**	Total cost	0	0	-	0.00	0
		Scheme amount		-	-			Scheme amount			-	0.00	
		Patient levy		-	-			Patient levy			-	0.00	

F = Female; M = male; U = unidentified.

Frequency = number of medicine items claimed per year.

% n = percentage items of total items claimed per gender group represented by biologic immunomodulators. (% n = $n_{biologics}/n_{total\ database}$).

SD = Standard Deviation.

% R = percentage of total medicine expenditure per gender group represented by biologic immunomodulators. (% R = Total $cost_{biologics}$/Total $cost_{total\ database}$).

Table A.17 Frequency and cost of biologic immunomodulators according to age group 1

AVERAGE COST PER MEDICINE ITEM							
Year	**Age group**	**Variable**	**Number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**1**	Total cost	53	3.01	6448.71 ± 1443.03	341,781.53	100.00
		Scheme amount			5865.40 ± 2107.78	310,865.94	90.95
		Patient levy			583.31 ± 1875.21	30,915.59	9.05
2006	**1**	Total cost	80	2.83	7361.81 ± 1483.94	588,945.03	100.00
		Scheme amount			7195.31 ± 1834.04	575,624.89	97.74
		Patient levy			166.50 ± 990.82	13,320.14	2.26
2007	**1**	Total cost	122	3.39	8465.29 ± 1300.49	1,032,765.46	100.00
		Scheme amount			8465.29 ± 1300.49	1,032,765.44	99.99
		Patient levy			0.00 ± 0.00	0.02	0.01
2008	**1**	Total cost	119	3.19	8357.97 ± 1169.97	994,598.45	100.00
		Scheme amount			8357.55 ± 1170.09	994,548.45	99.99
		Patient levy			0.42 ± 2.01	50.00	0.01
AVERAGE COST PER PRESCRIPTION							
Year	**Age group**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**1**	Total cost	53	4.02	6448.71 ± 1443.03	341,781.53	100.00
		Scheme amount			5865.40 ± 2107.78	310,865.94	90.95
		Patient levy			583.31 ± 1875.21	30,915.59	9.05
2006	**1**	Total cost	79	3.85	7455.00 ± 1401.56	588,945.03	100.00
		Scheme amount			7286.39 ± 1781.11	575,624.89	97.74
		Patient levy			168.61 ± 996.97	13,320.14	2.26
2007	**1**	Total cost	117	3.94	8827.06 ± 4168.25	1,032,765.46	100.00
		Scheme amount			8827.06 ± 4168.25	1,032,765.44	99.99
		Patient levy			0.00 ± 0.00	0.02	0.01
2008	**1**	Total cost	116	3.63	8574.12 ± 2043.46	994,598.45	100.00
		Scheme amount			8573.69 ± 2043.57	994,548.45	99.99
		Patient levy			0.43 ± 2.04	50.00	0.01

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Age group**	**Total number of prescriptions**	**Mean ± SD (Items)**	**Total number of medicine items**
2005	**1**	53	1.00 ± 0.00	53.00
2006	**1**	79	1.01 ± 0.11	80.00
2007	**1**	117	1.04 ± 0.30	122.00
2008	**1**	116	1.03 ± 0.16	119.00

Table A.18 Frequency and cost of biologic immunomodulators according to age group 2

AVERAGE COST PER MEDICINE ITEM							
Year	**Age group**	**Variable**	**Number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**2**	Total cost	321	18.25	5761.97 ± 1965.33	1,849,592.22	100.00
		Scheme amount			5477.07 ± 2173.25	1,758,138.28	95.06
		Patient levy			284.90 ± 1197.31	91,453.94	4.94
2006	**2**	Total cost	529	18.70	6807.05 ± 1489.33	3,600,929.33	100.00
		Scheme amount			6552.25 ± 1809.67	3,466,139.94	96.26
		Patient levy			254.80 ± 1131.15	134,789.39	3.74
2007	**2**	Total cost	609	16.94	7936.64 ± 7936.64	4,833,412.17	100.00
		Scheme amount			7721.53 ± 2170.48	4,702,409.75	97.30
		Patient levy			215.11 ± 1114.59	131,002.42	2.70
2008	**2**	Total cost	525	14.07	8562.36 ± 3980.14	4,495,237.57	100.00
		Scheme amount			8195.35 ± 4293.25	4,302,561.02	95.71
		Patient levy			367.00 ± 1591.24	192,676.55	4.29
AVERAGE COST PER PRESCRIPTION							
Year	**Age group**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**2**	Total cost	242	18.35	7642.94 ± 4262.52	1,849,592.22	100.00
		Scheme amount			7265.03 ± 4204.15	1,758,138.28	95.06
		Patient levy			377.91 ± 1366.81	91,453.94	4.94
2006	**2**	Total cost	463	22.54	7777.39 ± 3342.34	3,600,929.33	100.00
		Scheme amount			7486.26 ± 3514.56	3,466,139.94	96.26
		Patient levy			291.12 ± 1345.61	134,789.39	3.74
2007	**2**	Total cost	590	19.86	8192.22 ± 2592.25	4,833,412.17	100.00
		Scheme amount			7970.19 ± 2784.25	4,702,409.75	97.30
		Patient levy			222.04 ± 1159.22	131,002.42	2.70
2008	**2**	Total cost	507	15.88	8866.35 ± 4515.75	4,495,237.57	100.00
		Scheme amount			8486.31 ± 4772.72	4,302,561.02	95.71
		Patient levy			380.03 ± 1709.81	192,676.55	4.29

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Age group**	**Total number of prescriptions**	**Mean ± SD (Items)**	**Total number of medicine items**
2005	**2**	242	1.33 ± 0.77	321.00
2006	**2**	463	1.14 ± 0.53	529.00
2007	**2**	590	1.03 ± 0.18	609.00
2008	**2**	507	1.04 ± 0.19	525.00

Table A.19 Frequency and cost of biologic immunomodulators according to age group 3

AVERAGE COST PER MEDICINE ITEM							
Year	**Age group**	**Variable**	**Number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**3**	Total cost	899	51.11	5808.47 ± 2136.38	5,221,815.06	100.00
		Scheme amount			5578.17 ± 2307.20	5,014,776.95	96.04
		Patient levy			230.30 ± 1145.56	207,038.11	3.96
2006	**3**	Total cost	1,569	55.46	6922.75 ± 1937.75	10,861,791.51	100.00
		Scheme amount			6774.06 ± 2097.02	10,628,500.40	97.85
		Patient levy			148.69 ± 914.72	233,291.11	2.15
2007	**3**	Total cost	2,028	56.41	8839.32 ± 4115.13	17,926,142.99	100.00
		Scheme amount			8578.33 ± 4318.61	17,396,857.49	97.05
		Patient levy			260.99 ± 1512.32	529,285.50	2.95
2008	**3**	Total cost	2,194	58.80	9515.61 ± 6186.06	20,877,237.75	100.00
		Scheme amount			9351.79 ± 6259.26	20,517,833.75	98.28
		Patient levy			163.81 ± 1156.45	359,404.00	1.72
AVERAGE COST PER PRESCRIPTION							
Year	**Age group**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**3**	Total cost	743	56.33	7028.01 ± 3631.55	5,221,815.06	100.00
		Scheme amount			6749.36 ± 3804.95	5,014,776.95	96.04
		Patient levy			278.65 ± 1314.00	207,038.11	3.96
2006	**3**	Total cost	1,190	57.94	9127.56 ± 4550.21	10,861,791.51	100.00
		Scheme amount			8931.51 ± 4705.71	10,628,500.40	97.85
		Patient levy			196.04 ± 1050.36	233,291.11	2.15
2007	**3**	Total cost	1,723	57.99	10404.03 ± 6634.42	17,926,142.99	100.00
		Scheme amount			10096.84 ± 6811.61	17,396,857.49	97.05
		Patient levy			307.19 ± 1774.45	529,285.50	2.95
2008	**3**	Total cost	1,941	60.79	10755.92 ± 8149.51	20,877,237.75	100.00
		Scheme amount			10570.75 ± 8198.35	20,517,833.75	98.28
		Patient levy			185.16 ± 1244.32	359,404.00	1.72
AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION							
Year		**Age group**	**Total number of prescriptions**		**Mean ± SD (Items)**	**Total number of medicine items**	
2005		**3**	743		1.21 ± 0.60	899.00	
2006		**3**	1,190		1.32 ± 0.74	1,569.00	
2007		**3**	1,723		1.18 ± 0.46	2028.00	
2008		**3**	1,941		1.13 ± 0.37	2194.00	

Table A.20 Frequency and cost of biologic immunomodulators according to age group 4

AVERAGE COST PER MEDICINE ITEM							
Year	**Age group**	**Variable**	**Number of medicine items**	**% items**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**4**	Total cost	486	27.63	5024.63 ± 2298.81	2,441,972.20	100.00
		Scheme amount			4963.11 ± 2332.66	2,412,070.17	98.78
		Patient levy			61.53 ± 454.41	29,902.03	1.22
2006	**4**	Total cost	651	23.01	5990.03 ± 2330.47	3,899,510.82	100.00
		Scheme amount			5974.14 ± 2340.31	3,889,167.05	99.73
		Patient levy			15.89 ± 248.17	10,343.77	0.27
2007	**4**	Total cost	836	23.25	8667.60 ± 4291.89	7,246,117.38	100.00
		Scheme amount			8454.78 ± 4410.10	7,068,193.89	97.54
		Patient levy			212.83 ± 1450.56	177,923.49	2.46
2008	**4**	Total cost	893	23.93	10525.43 ± 6563.89	9,399,212.65	100.00
		Scheme amount			10366.66 ± 6624.95	9,257,423.35	98.49
		Patient levy			158.78 ± 1188.25	141,789.30	1.51
AVERAGE COST PER PRESCRIPTION							
Year	**Age group**	**Variable**	**Number of prescriptions**	**% Rx**	**Mean ± SD (R)**	**Total cost (R)**	**%**
2005	**4**	Total cost	281	21.30	8690.29 ± 6455.77	2,441,972.20	100.00
		Scheme amount			8583.88 ± 6525.72	2,412,070.17	98.78
		Patient levy			106.41 ± 694.24	29,902.03	1.22
2006	**4**	Total cost	322	15.68	12110.28 ± 7203.67	3,899,510.82	100.00
		Scheme amount			12078.16 ± 7199.91	3,889,167.05	99.73
		Patient levy			32.12 ± 357.11	10,343.77	0.27
2007	**4**	Total cost	541	18.21	13393.93 ± 7391.54	7,246,117.38	100.00
		Scheme amount			13065.05 ± 7425.60	7,068,193.89	97.54
		Patient levy			328.88 ± 2240.25	177,923.49	2.46
2008	**4**	Total cost	629	19.70	14943.10 ± 12614.05	9,399,212.65	100.00
		Scheme amount			14717.68 ± 12590.63	9,257,423.35	98.49
		Patient levy			225.42 ± 1774.19	141,789.30	1.51

AVERAGE NUMBER OF MEDICINE ITEMS PER PRESCRIPTION				
Year	**Age group**	**Total number of prescriptions**	**Mean ± SD (Items)**	**Total number of medicine items**
2005	**4**	281	1.73 ± 1.09	486.00
2006	**4**	322	2.02 ± 1.19	651.00
2007	**4**	541	1.55 ± 0.66	836.00
2008	**4**	629	1.42 ± 0.57	893.00

A.21 Average cost per medicine item according to age: total database vs target population

AVERAGE COST PER MEDICINE ITEM ACCORDING TO AGE FOR TOTAL DATABASE						AVERAGE COST PER MEDICINE ITEM ACCORDING TO AGE FOR BIOLOGIC IMMUNOMODULATORS							
Year	Age group	Variable	Frequency (n)	Mean ± SD (R)	Total cost (R)	Year	Age group	Variable	Frequency (n)	% n	Mean ± SD (R)	Total cost (R)	% R
2005	1	Total cost	3,658,580	65.54 ± 101.13	239,766,846.41	2005	1	Total cost	53	0.001	6448.71 ± 1443.03	341,781.53	0.143
		Scheme amount		58.74 ± 95.32	214,897,939.98			Scheme amount			5865.40 ± 2107.78	310,865.94	
		Patient levy		6.80 ± 29.14	24,868,906.43			Patient levy			583.31 ± 1875.21	30,915.59	
	2	Total cost	2,930,322	77.40 ± 148.62	226,818,610.94		2	Total cost	321	0.011	5761.97 ± 1965.33	1,849,592.22	0.815
		Scheme amount		70.12 ± 142.95	205,479,491.44			Scheme amount			5477.07 ± 2173.25	1,758,138.28	
		Patient levy		7.28 ± 36.32	21,339,119.50			Patient levy			284.90 ± 1197.31	91,453.94	
	3	Total cost	8,363,409	97.08 ± 176.48	811,952,830.36		3	Total cost	899	0.011	5808.47 ± 2136.38	5,221,815.06	0.643
		Scheme amount		86.21 ± 169.38	721,025,658.60			Scheme amount			5578.17 ± 2307.20	5,014,776.95	
		Patient levy		10.87 ± 45.59	90,927,171.76			Patient levy			230.30 ± 1145.56	207,038.11	
	4	Total cost	4,548,463	119.01 ± 193.54	541,326,963.92		4	Total cost	486	0.011	5024.63 ± 2298.81	2,441,972.20	0.451
		Scheme amount		101.36 ± 185.77	461,044,559.41			Scheme amount			4963.11 ± 2332.66	2,412,070.17	
		Patient levy		17.65 ± 47.19	80,282,404.51			Patient levy			61.53 ± 454.41	29,902.03	
2006	1	Total cost	3,912,699	64.95 ± 113.93	254,141,563.62	2006	1	Total cost	80	0.002	7361.81 ± 1483.94	588,945.03	0.232
		Scheme amount		56.77 ± 107.71	222,111,395.73			Scheme amount			7195.31 ± 1834.04	575,624.89	
		Patient levy		8.19 ± 33.36	32,030,167.89			Patient levy			166.50 ± 990.82	13,320.14	
	2	Total cost	3,068,900	76.47 ± 169.84	234,674,113.15		2	Total cost	529	0.017	6807.05 ± 1489.33	3,600,929.33	1.534
		Scheme amount		67.96 ± 163.44	208,554,713.53			Scheme amount			6552.25 ± 1809.67	3,466,139.94	
		Patient levy		8.51 ± 41.72	26,119,399.62			Patient levy			254.80 ± 1131.15	134,789.39	
	3	Total cost	9,261,669	96.15 ± 209.04	890,470,151.20		3	Total cost	1,569	0.017	6922.75 ± 1937.75	10,861,791.51	1.220
		Scheme amount		84.33 ± 203.00	781,008,788.47			Scheme amount			6774.06 ± 2097.02	10,628,500.40	
		Patient levy		11.82 ± 46.52	109,461,362.73			Patient levy			148.69 ± 914.72	233,291.11	
	4	Total cost	4,870,154	119.19 ± 232.49	580,452,906.12		4	Total cost	651	0.013	5990.03 ± 2330.47	3,899,510.82	0.672
		Scheme amount		100.00 ± 225.84	487,035,053.63			Scheme amount			5974.14 ± 2340.31	3,889,167.05	

		Patient levy		19.18 ± 52.07	93,417,852.49			Patient levy			15.89 ± 248.17	10,343.77	
2007	**1**	Total cost	3,346,576	68.42 ± 163.51	228,982,535.62	*2007*	**1**	Total cost	122	0.004	8465.29 ± 1300.49	1,032,765.46	0.451
		Scheme amount		57.11 ± 146.54	191,117,985.47			Scheme amount			8465.29 ± 1300.49	1,032,765.44	
		Patient levy		11.31 ± 66.36	37,864,550.15			Patient levy			0.00 ± 0.00	0.02	
	2	Total cost	2,528,016	81.77 ± 263.69	206,723,414.80		**2**	Total cost	609	0.024	7936.64 ± 7936.64	4,833,412.17	2.338
		Scheme amount		69.79 ± 252.80	176,421,796.24			Scheme amount			7721.53 ± 2170.48	4,702,409.75	
		Patient levy		11.99 ± 66.83	30,301,618.56			Patient levy			215.11 ± 1114.59	131,002.42	
	3	Total cost	8,494,142	103.40 ± 353.70	878,327,951.34		**3**	Total cost	2,028	0.024	8839.32 ± 4115.13	17,926,142.99	2.041
		Scheme amount		88.40 ± 334.16	750,921,044.36			Scheme amount			8578.33 ± 4318.61	17,396,857.49	
		Patient levy		15.00 ± 101.86	127,406,906.98			Patient levy			260.99 ± 1512.32	529,285.50	
	4	Total cost	4,706,990	128.37 ± 376.68	604,250,274.90		**4**	Total cost	836	0.018	8667.60 ± 4291.89	7,246,117.38	1.200
		Scheme amount		105.49 ± 350.11	496,546,206.85			Scheme amount			8454.78 ± 4410.10	7,068,193.89	
		Patient levy		22.88 ± 131.19	107,704,068.05			Patient levy			212.83 ± 1450.56	177,923.49	
2008	**1**	Total cost	2,421,518	75.49 ± 210.85	182,794,294.08	*2008*	**1**	Total cost	119	0.005	8357.97 ± 1169.97	994,598.45	0.588
		Scheme amount		61.95 ± 201.09	150,022,179.26			Scheme amount			8357.55 ± 1170.09	994,548.45	
		Patient levy		13.53 ± 51.49	32,772,114.82			Patient levy			0.42 ± 2.01	50.00	
	2	Total cost	1,876,874	90.16 ± 363.99	169,227,300.16		**2**	Total cost	525	0.028	8562.36 ± 3980.14	4,495,237.57	2.656
		Scheme amount		75.70 ± 345.02	142,085,583.63			Scheme amount			8195.35 ± 4293.25	4,302,561.02	
		Patient levy		14.46 ± 97.47	27,141,716.53			Patient levy			367.00 ± 1591.24	192,676.55	
	3	Total cost	7,639,419	109.54 ± 466.22	836,842,632.27		**3**	Total cost	2,194	0.029	9515.61 ± 6186.06	20,877,237.75	2.495
		Scheme amount		92.09 ± 450.59	703,481,122.70			Scheme amount			9351.79 ± 6259.26	20,517,833.75	
		Patient levy		17.46 ± 109.70	133,361,509.57			Patient levy			163.81 ± 1156.45	359,404.00	
	4	Total cost	4,501,442	132.63 ± 497.24	597,006,787.34		**4**	Total cost	893	0.020	10525.43 ± 6563.89	9,399,212.65	1.574
		Scheme amount		107.29 ± 476.82	482,959,343.33			Scheme amount			10366.66 ± 6624.95	9,257,423.35	
		Patient levy		25.34 ± 126.73	114,047,444.01			Patient levy			158.78 ± 1188.25	141,789.30	

Age group 1 = < 25 years; Age group 2 = 25-39 years; Age group 3 = 40-64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

% n = percentage items of total items claimed per gender group represented by biologic immunomodulators. (% n = $n_{biologics}/n_{total\ database}$).

% R = percentage of total medicine expenditure per gender group represented by biologic immunomodulators. (% R = Total $cost_{biologics}$/Total $cost_{total\ database}$).

A.22.1 Combinations prescribed during phase 1 of RA treatment

MEDICINE ITEMS				N
Combination of 2 items				
Methotrexate	Folic acid			39.00
Aspirin	Atorvastatin			18.00
Methotrexate	Sulphasalazine			17.00
Phenytoin	Phenytoin			14.00
Sulphasalazine	Prednisolone			12.00
Bethametasone	Diclofenac			11.00
Amlodipine	Ramipril			10.00
Methotrexate	Prednisolone			10.00
Chloroquine	Sulphasalazine			9.00
Methotrexate	Ibuprofen			9.00
Perindopril	Atorvastatin			9.00
Combination of 3 items				
Meloxicam	Methotrexate	Sulphasalazine		37.00
Bisoprolol	Rosuvastatin	Valsartan		9.00
Meloxicam	Methotrexate	Prednisolone		9.00
Folic acid	Celecoxib	Methotrexate		8.00
Folic acid	Methotrexate	Diclofenac		7.00
Leflunomide	Folic acid	Methotrexate		7.00
Meloxicam	Methotrexate	Trandolapril/Verapamil		7.00
Methotrexate	Perindopril	Allopurinol		7.00
Aspirin	Atorvastatin	Sulphasalazine		6.00
Folic acid	Methotrexate	Prednisolone		6.00
Methotrexate	Chloroquine	Sulphasalazine		6.00
Combination of 4 items				
Celecoxib	Perindopril	Bezafibrate	Atenolol	15.00
Folic acid	Methotrexate	Chloroquine	Sulphasalazine	13.00
Bisoprolol	Rosuvastatin	Valsartan	Aspirin	7.00
Bisoprolol	Aspirin	Atorvastatin	Perindopril	6.00
Indomethacin	Prednisolone	Methotrexate	Chloroquine	6.00
Methylprednisolone	Bupivacaine	Llignocaine	Sterile water/Inj/Inf	6.00
Omeprazole	Bisoprolol	Thyroxine	Methotrexate	6.00
Estradiol/Norethisterol	Amlodipine	Calcium Chloride/Glucose	Prednisolone	5.00
Methotrexate	Prednisolone	Par/Dextro/Diphen/Caff	Zolpidem	5.00
Atenolol	Fluoxetine	Bromazepam	Par/Cod/Caff/Mepro	4.00
n = frequency with which specific combination was prescribed during four years				

Table A.22.2.1 Combinations prescribed during phase 2 of RA treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
Folic acid	Methotrexate			66.00
Meloxicam	Methotrexate			47.00
Amlodidpine	Simvastatin			16.00
Methotrexate	Chloroquine			13.00
Meloxicam	Aspirin			11.00
Alendronate	Methotrexate			10.00
Celecoxib	Methotrexate			10.00
Folic acid	Meloxicam			9.00
Lumiracoxib	Sulphasalazine			9.00
Thyroxine	Alendronate			9.00
Combination of 3 items per prescription				
Meloxicam	Folic acid	Methotrexate		17.00
Prednisolone	Folic acid	Methotrexate		15.00
Celecoxib	Folic acid	Methotrexate		13.00
Methotrexate	Folic acid	Chloroquine		13.00
Meloxicam	Prednisolone	ASPIRIN		10.00
Prednisolone	Methotrexate	Par/Dextro/Diphen/Caff		9.00
Thyroxine	Folic acid	Thyroxine		7.00
Methotrexate	Folic acid	Diclofenac		6.00
Rosuvastatin	Folic acid	Methotrexate		6.00
Aspirin	Quinapril/Hydrochlorthiazide	Diclofenac		6.00
Combination of 4 items per prescription				
Methotrexate	Celecoxib	Prednisolone	Folic acid	22.00
Calcipotriol	Celecoxib	Sulphasalazine	Leflunomide	14.00
Perindopril	Celecoxib	Atenolol	Bezafibrate	13.00
Methotrexate	Calcipotriol	Naproxen	Folic acid	13.00
Celecoxib	Prednisolone	Methotrexate	Folic acid	12.00
Methotrexate	Folic acid	Diclofenac	Irbesartan	12.00
Sulphasalazine	Thyroxine	Venlafaxine	Celecoxib	11.00
Methotrexate	Prednisolone	Lumiracoxib	Folic acid	8.00
Bisoprolol	Celecoxib	Methotrexate	Folic acid	6.00
Prednisolone	Methotrexate	Diclofenac	Folic acid	6.00
n = frequency with which specific combination was prescribed during four years				

Table A.22.2.2 Combinations of biologic immunomodulators prescribed during phase 2

MEDICINE ITEMS			n
1 biologic immunomodulator per prescription			
Adalimumab			694.00
Etanercept			1643.00
Infliximab			81.00
Rituximab			1.00
Combinations of 2 biologic immunomodulators per prescription			
Adalimumab	Adalimumab		12.00

Etanercept	Etanercept			44.00
Infliximab	Infliximab			6.00
Combinations of 3 biologic immunomodulators per prescription				
Etanercept	Etanercept	Etanercept		5.00
Infliximab	Infliximab	Infliximab		1.00
4 biologic immunomodulators per prescription				
Etanercept	Etanercept	Etanercept	Etanercept	1.00
n = frequency with which specific combination was prescribed during four years				

Table A.22.3 Combinations prescribed during phase 3 of RA treatment

MEDICINE ITEMS				**n**
Combination of 2 items				
Bisoprolol	Celecoxib			20.00
Calcium Ccarbonate/magnesium	Alendronate			14.00
Prednisolone	Meloxicam			10.00
Sodium chloride	Hydrocortisone			10.00
Leflunomide	Medroxyprogesterone			9.00
Leflunomide	Candesartan cilexetil			8.00
Diclofenac	Prednisolone			7.00
Thyroxine	Propranolol			7.00
Bisoprolol	ASPIRIN			6.00
Candesartan cilexetil	Prednisone			6.00
Combination of 3 items				
Folic acid	Prednisolone	Methotrexate		16.00
Naproxen	Methotrexate	Sulphasalazine		9.00
Celecoxib	Bisoprolol	Chloroquine		5.00
Lansoprazole	Celecoxib	Atenolol		4.00
Diclofenac	Folic acid	Prednisolone		4.00
Methotrexate	Folic acid	Prednisolone		4.00
Methotrexate	Folic acid	Sulphasalazine		4.00
Candesartan cilexetil	Leflunomide	Oestradiol		4.00
Amitriptyline	Paroxetine	Felodipine/ramipril		4.00
Propranolol	Thyroxine	Valsartan		4.00
Combination of 4 items				
Leflunomide	Methotrexate	Celecoxib	Folic acid	18.00
Leflunomide	Methotrexate	Meloxicam	Folic acid	6.00
Celecoxib	Atenolol	Prednisolone	Thyroxine	4.00
Folic acid	Clopidrogel	Methotrexate	Atorvastatin	4.00
Folic acid	Methotrexate	Bisoprolol	Celecoxib	4.00
Atorvastatin	Perindopril	Methotrexate	Aspirin	3.00
Folic acid	Amitriptyline	Prednisolone	Diclofenac	3.00
Methylprednisolone	Sterile water/inj/inf	Lignocaine	Bupivacaine	3.00
Omeprazole	Oestradiol	Methotrexate	Thyroxine	3.00
Prednisolone	Methotrexate	Folic acid	Celecoxib	3.00
Prednisolone	Torazemide	Spironolactione	Sulphasalazine	3.00
n = frequency with which specific combination was prescribed during four years				

Table A.23.1.1 Average cost per medicine item for Rheumatoid Arthritis patients

Phase	Variables	Frequency (n)	Mean ± SD	Total cost	%
Phase 1	Total cost	17,550	128.45 ± 155.93	2,254,330.44	100.00
	Scheme amount		104.47 ± 141.87	1,833,469.09	81.33
	Patient levy		23.98 ± 60.59	420,861.35	18.67
Phase 2	Total cost	15,011	1477.88 ± 3134.39	22,184,429.98	100.00
	Scheme amount		1409.75 ± 3072.85	21,161,818.13	95.39
	Patient levy		68.12 ± 609.82	1,022,611.85	4.61
Phase 3	Total cost	5,001	198.67 ± 888.31	993,533.62	100.00
	Scheme amount		155.32 ± 600.33	776,761.35	78.18
	Patient levy		43.35 ± 644.15	216,772.27	21.82

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.1.2 Average cost per medicine item for Rheumatoid Arthritis patients during phase 2

Phase	Medicines	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	***Biologics***	Total cost	2,565	17.08	8073.61 ± 2210.46	20,708,818.86	100.00
		Scheme amount			7785.83 ± 2470.84	19,970,653.39	96.44
		Patient levy			287.78 ± 1450.33	738,165.47	3.56
	Other	Total cost	12,446	82.91	118.56 ± 168.24	1,475,611.12	100.00
		Scheme amount			95.71 ± 157.27	1,191,164.74	80.72
		Patient levy			22.85 ± 56.27	284,446.38	19.28

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of total number of items claimed during phase 2.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.2.1 Average cost per medicine item for Rheumatoid Arthritis patients according to gender

Phase	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	**F**	Total cost	12,593	71.75	123.76 ± 150.57	1,558,459.11	100.00
		Scheme amount			100.41 ± 132.93	1,264,516.79	81.14
		Patient levy			23.34 ± 59.61	293,942.32	18.86
	M	Total cost	4,957	28.25	140.38 ± 168.21	695,871.33	100.00
		Scheme amount			114.78 ± 161.92	568,952.30	81.76
		Patient levy			25.60 ± 62.99	126,919.03	18.24
Phase 2	**F**	Total cost	11,733	78.16	1384.71 ± 3039.15	16,246,745.95	100.00
		Scheme amount			1324.87 ± 2984.09	15,544,670.28	95.68
		Patient levy			59.84 ± 553.74	702,075.67	4.32
	M	Total cost	3,278	22.84	1811.37 ± 3433.68	5,937,684.03	100.00
		Scheme amount			1713.59 ± 3354.36	5,617,147.85	94.60
		Patient levy			97.78 ± 777.47	320,536.18	5.40

Phase 3	**F**	Total cost	3,059	61.17	202.98 ± 1045.15	620,914.27	100.00
		Scheme amount			152.48 ± 627.31	466,439.63	75.12
		Patient levy			50.50 ± 820.78	154,474.64	24.88
	M	Total cost	1,942	38.03	191.87 ± 558.30	372,619.35	100.00
		Scheme amount			159.79 ± 555.32	310,321.72	83.28
		Patient levy			32.08 ± 85.27	62,297.63	16.72

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of total number of items claimed in each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.2.2 Average cost per medicine item for Rheumatoid Arthritis patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	***Biologics***	**F**	Total cost	1,897	73.96	7971.87 ± 2285.47	15,122,642.28	100.00
			Scheme amount			7714.33 ± 2499.79	14,634,079.91	96.77
			Patient levy			257.54 ± 1355.47	488,562.37	3.23
		M	Total cost	668	26.04	8362.54 ± 1954.94	5,586,176.58	100.00
			Scheme amount			7988.88 ± 2376.83	5,336,573.48	95.53
			Patient levy			373.66 ± 1689.14	249,603.10	4.47
	Other	**F**	Total cost	9,836	79.03	114.28 ± 165.93	1,124,103.67	100.00
			Scheme amount			92.58 ± 156.70	910,590.37	81.01
			Patient levy			21.71 ± 50.86	213,513.30	18.99
		M	Total cost	2,610	20.97	134.68 ± 175.80	351,507.45	100.00
			Scheme amount			107.50 ± 158.88	280,574.37	79.82
			Patient levy			27.18 ± 73.01	70,933.08	20.18

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of total biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.3.1 Average cost per medicine item for Rheumatoid Arthritis patients according to age

Phase	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	1	Total cost	209	1.19	92.63 ± 86.26	19,359.05	100.00
		Scheme amount			67.77 ± 71.28	14,163.98	73.16
		Patient levy			24.86 ± 30.83	5,195.07	26.84
	2	Total cost	1,441	8.21	110.13 ± 147.76	158,690.67	100.00
		Scheme amount			96.54 ± 135.84	139,113.42	87.66
		Patient levy			13.59 ± 57.17	19,577.25	12.34
	3	Total cost	11,027	62.83	137.23 ± 163.05	1,513,263.24	100.00
		Scheme amount			113.52 ± 149.92	1,251,747.50	82.72
		Patient levy			23.72 ± 61.46	261,515.74	17.28
	4	Total cost	4,873	27.77	115.54 ± 141.94	563,017.48	100.00
		Scheme amount			87.92 ± 124.18	428,444.19	76.10
		Patient levy			27.62 ± 60.18	134,573.29	23.90
Phase 2	1	Total cost	215	1.43	2213.06 ± 3597.53	475,807.33	100.00
		Scheme amount			2203.19 ± 3603.32	473,686.50	99.55
		Patient levy			9.86 ± 17.28	2,120.83	0.45
	2	Total cost	1,811	12.06	1712.26 ± 3093.36	3,100,911.59	100.00
		Scheme amount			1548.29 ± 2909.72	2,803,955.16	90.42
		Patient levy			163.97 ± 1028.95	296,956.43	9.58
	3	Total cost	9,315	62.05	1515.66 ± 3206.92	14,118,352.00	100.00
		Scheme amount			1463.28 ± 3166.18	13,630,473.61	96.54
		Patient levy			52.38 ± 476.65	487,878.39	3.46
	4	Total cost	3,670	24.45	1223.26 ± 2912.37	4,489,359.06	100.00
		Scheme amount			1159.05 ± 2851.36	4,253,702.86	94.75
		Patient levy			64.21 ± 645.70	235,656.20	5.25
Phase 3	1	Total cost	342	6.84	550.37 ± 1110.69	188,226.72	100.00
		Scheme amount			444.95 ± 1011.89	152,172.97	80.85
		Patient levy			105.42 ± 173.98	36,053.75	19.15
	2	Total cost	501	10.02	101.01 ± 128.22	50,604.74	100.00
		Scheme amount			76.44 ± 110.95	38,298.86	75.68
		Patient levy			24.56 ± 65.23	12,305.88	24.32
	3	Total cost	3,402	68.03	189.82 ± 1007.24	645,778.67	100.00
		Scheme amount			147.01 ± 641.51	500,125.93	77.45
		Patient levy			42.81 ± 777.70	145,652.74	22.55
	4	Total cost	756	15.12	144.08 ± 148.37	108,923.49	100.00
		Scheme amount			113.97 ± 134.87	86,163.59	79.10
		Patient levy			30.11 ± 68.65	22,759.90	20.90

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of total number of items claimed in each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.3.2 Average cost per medicine item for Rheumatoid Arthritis patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Final total cost	61	2.38	7586.36 ± 2273.98	462,768.07	100.00
			Final scheme cost			7586.36 ± 2273.98	462,768.07	100.00
			Final levy			0.00 ± 0.00	0.00	0.00
		2	Final total cost	414	16.14	7036.27 ± 2226.98	2,913,014.56	100.00
			Final scheme cost			6366.75 ± 2610.58	2,635,834.00	90.48
			Final levy			669.52 ± 2071.37	277,180.56	9.52
		3	Final total cost	1,599	62.34	8249.13 ± 2241.64	13,190,351.27	100.00
			Final scheme cost			8053.43 ± 2415.16	12,877,440.28	97.63
			Final levy			195.69 ± 1133.95	312,910.99	2.37
		4	Final total cost	491	19.14	8437.24 ± 1787.44	4,142,684.96	100.00
			Final scheme cost			8135.66 ± 2117.27	3,994,611.04	96.43
			Final levy			301.58 ± 1742.31	148,073.92	3.57
	Other	1	Final total cost	154	1.24	84.67 ± 58.83	13,039.26	100.00
			Final scheme cost			70.90 ± 52.82	10,918.43	83.74
			Final levy			13.77 ± 19.07	2,120.83	16.26
		2	Final total cost	1,397	11.22	134.50 ± 205.53	187,897.03	100.00
			Final scheme cost			120.34 ± 187.55	168,121.16	89.48
			Final levy			14.16 ± 71.59	19,775.87	10.52
		3	Final total cost	7,716	62.00	120.27 ± 175.03	928,000.73	100.00
			Final scheme cost			97.59 ± 166.19	753,033.33	81.15
			Final levy			22.68 ± 53.00	174,967.40	18.85
		4	Final total cost	3,179	25.54	109.05 ± 132.23	346,674.10	100.00
			Final scheme cost			81.50 ± 117.12	259,091.82	74.74
			Final levy			27.55 ± 57.01	87,582.28	25.26

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of total biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.4.1 Average cost per medicine item for Rheumatoid Arthritis patients according to prescriber

Phase	Prescriber	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	1	Total cost	6,743	38.42	113.44 ± 122.99	764,948.82	100.00
		Scheme amount			91.19 ± 112.20	614,873.38	80.83
		Patient levy			22.26 ± 49.23	150,075.44	19.62
	2	Total cost	339	1.93	237.68 ± 307.46	80,572.97	100.00
		Scheme amount			195.70 ± 261.64	66,342.45	82.34
		Patient levy			41.98 ± 90.19	14,230.52	17.66
	3	Total cost	3,477	19.87	131.70 ± 170.14	457,914.48	100.00
		Scheme amount			106.24 ± 157.78	369,410.27	80.67
		Patient levy			25.45 ± 66.29	88,504.21	19.33
	4	Total cost	6,959	39.65	135.66 ± 162.82	944,086.73	100.00
		Scheme amount			111.68 ± 148.23	777,169.46	82.32
		Patient levy			23.99 ± 65.48	166,917.27	17.68
	5	Total cost	32	1.83	212.73 ± 217.86	6,807.44	100.00
		Scheme amount			177.30 ± 196.57	5,673.53	83.34
		Patient levy			35.43 ± 49.44	1,133.91	16.66
Phase 2	1	Total cost	3,817	25.43	474.02 ± 1753.57	1,809,347.24	100.00
		Scheme amount			434.53 ± 1692.97	1,658,592.50	91.67
		Patient levy			39.50 ± 319.68	150,754.74	8.33
	2	Total cost	94	0.63	95.18 ± 106.46	8,946.91	100.00
		Scheme amount			58.06 ± 77.36	5,457.27	61.00
		Patient levy			37.12 ± 94.60	3,489.64	39.00
	3	Total cost	1,995	13.29	534.28 ± 1737.03	1,065,898.39	100.00
		Scheme amount			492.95 ± 1655.46	983,431.49	92.26
		Patient levy			41.34 ± 346.46	82,466.90	7.74
	4	Total cost	9,090	60.56	2120.93 ± 3633.37	19,279,275.36	100.00
		Scheme amount			2034.48 ± 3574.60	18,493,379.46	95.92
		Patient levy			86.46 ± 737.53	785,895.90	4.08
	5	Total cost	15	0.10	1397.47 ± 3423.22	20,962.08	100.00
		Scheme amount			1397.16 ± 3423.35	20,957.41	99.98
		Patient levy			0.31 ± 1.21	4.67	0.02
Phase 3	1	Total cost	2,051	41.01	188.70 ± 501.90	387,018.14	100.00
		Scheme amount			151.76 ± 482.02	311,255.60	80.42
		Patient levy			36.94 ± 88.46	75,762.54	19.58
	2	Total cost	22	0.44	307.97 ± 429.16	6,775.35	100.00
		Scheme amount			288.58 ± 432.43	6,348.83	93.70
		Patient levy			19.39 ± 17.32	426.52	6.30
	3	Total cost	1,073	21.46	221.79 ± 1633.83	237,982.00	100.00
		Scheme amount			144.77 ± 873.46	155,343.07	65.28
		Patient levy			77.02 ± 1380.45	82,638.93	34.72
	4	Total cost	1,722	34.43	136.82 ± 165.83	235,609.22	100.00
		Scheme amount			114.24 ± 158.48	196,722.53	83.50
		Patient levy			22.58 ± 52.53	38,886.69	16.50
	5	Total cost	126	2.52	831.75 ± 1355.23	104,800.66	100.00
		Scheme amount			681.86 ± 1239.11	85,914.54	81.98
		Patient levy			149.89 ± 225.51	18,886.12	18.02

	6	Total cost	7	0.14	3049.75 ± 5349.33	21,348.25	100.00
		Scheme amount			3025.25 ± 5365.30	21,176.78	99.20
		Patient levy			24.50 ± 41.08	171.47	0.80

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

Frequency = number of medicine items claimed per year. SD = Standard Deviation.

% items = % of total number of items claimed in each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.23.4.2 Average cost per medicine item for Rheumatoid Arthritis patients during phase 2 according to prescriber

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	170	6.63	8269.12 ± 2280.26	1,405,750.01	100.00
			Scheme amount			7933.18 ± 2306.13	1,348,640.91	95.94
			Patient levy			335.94 ± 1465.65	57,109.10	4.06
		2	Total cost	0	-	0.00 ± 0.00	0.00	0.00
			Scheme amount			0.00 ± 0.00	0.00	0.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		3	Total cost	125	4.87	6823.21 ± 2402.76	852,900.86	100.00
			Scheme amount			6463.56 ± 2356.25	807,944.85	94.73
			Patient levy			359.65 ± 1334.22	44,956.01	5.27
		4	Total cost	2,268	88.42	8126.33 ± 2174.46	18,430,511.99	100.00
			Scheme amount			7845.86 ± 2469.70	17,794,411.63	96.55
			Patient levy			280.47 ± 1456.34	636,100.36	3.45
		5	Total cost	2	0.08	9828.00 ± 0.00	19,656.00	100.00
			Scheme amount			9828.00 ± 0.00	19,656.00	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
	Other	1	Total cost	3,647	29.30	110.67 ± 110.16	403,597.23	100.00
			Scheme amount			84.99 ± 96.29	309,951.59	76.80
			Patient levy			25.68 ± 55.66	93,645.64	23.20
		2	Total cost	94	0.76	95.18 ± 106.46	8,946.91	100.00
			Scheme amount			58.06 ± 77.36	5457.27	61.00
			Patient levy			37.12 ± 94.60	3,489.64	39.00
		3	Total cost	1,870	15.02	113.90 ± 118.50	212,997.53	100.00
			Scheme amount			93.84 ± 109.29	175,486.64	82.39
			Patient levy			20.06 ± 52.20	37,510.89	17.61
		4	Total cost	6,822	54.81	124.42 ± 202.65	848,763.37	100.00
			Scheme amount			102.46 ± 191.53	698,967.83	82.85
			Patient levy			21.96 ± 56.93	149,795.54	17.65
		5	Total cost	13	0.10	100.47 ± 58.75	1,306.08	100.00
			Scheme amount			100.11 ± 59.26	1,301.41	99.64
			Patient levy			0.36 ± 1.30	4.67	0.36

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

Frequency = number of medicine items claimed per year. SD = Standard Deviation.

% items = % of total biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.1.1 Average cost per prescription for Rheumatoid Arthritis patients

Phase	Variables	Frequency (n)	Mean ± SD	Total cost	%
Phase 1	Total cost	6,271	359.49 ± 380.04	2,254,330.44	100.00
	Scheme amount		292.37 ± 331.37	1,833,469.09	81.33
	Patient levy		67.11 ± 143.79	420,861.35	18.67
Phase 2	Total cost	7,131	3110.98 ± 4146.23	22,184,429.98	100.00
	Scheme amount		2967.58 ± 4052.18	21,161,818.13	95.39
	Patient levy		143.40 ± 982.86	1,022,611.85	4.61
Phase 3	Total cost	2,120	468.65 ± 1575.84	993,533.62	100.00
	Scheme amount		366.40 ± 1179.01	776,761.35	78.18
	Patient levy		102.25 ± 994.57	2,167,72.27	21.82

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.1.2 Average cost per prescription for Rheumatoid Arthritis patients during phase 2

Phase	Medicines	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	Total cost	2,480	34.78	8350.33 ± 2651.65	20,708,818.86	100.00
		Scheme amount			8052.68 ± 2707.05	19,970,653.39	96.44
		Patient levy			297.65 ± 1645.76	738,165.47	3.56
	Other	Total cost	4,651	65.22	317.27 ± 405.49	1,475,611.12	100.00
		Scheme amount			256.11 ± 355.11	1,191,164.74	80.72
		Patient levy			61.16 ± 133.46	284,446.38	19.28

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = percentage of total number of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.2.1 Average cost per prescription for Rheumatoid Arthritis patient according to gender

Phase	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	**F**	Total cost	4,367	69.64	356.87 ± 376.48	1,558,459.11	100.00
		Scheme amount			289.56 ± 315.46	1,264,516.79	81.14
		Patient levy			67.31 ± 145.96	293,942.32	18.86
	M	Total cost	1,904	30.36	365.48 ± 388.11	695,871.33	100.00
		Scheme amount			298.82 ± 365.26	568,952.30	81.76
		Patient levy			66.66 ± 138.70	126,919.03	18.24
Phase 2	**F**	Total cost	5,473	76.75	2968.53 ± 4076.01	16,246,745.95	100.00
		Scheme amount			2840.25 ± 3979.58	15,544,670.28	95.68
		Patient levy			2968.53 ± 4076.01	702,075.67	4.32
	M	Total cost	1,658	23.25	3581.23 ± 4338.20	5,937,684.03	100.00
		Scheme amount			3387.91 ± 4257.40	5,617,147.85	94.60
		Patient levy			3581.23 ± 4338.20	320,536.18	5.40
	F	Total cost	1,403	66.18	442.56 ± 1726.04	620,914.27	100.00
		Scheme amount			332.46 ± 1159.84	27,831.13	75.12

Phase 3		Patient levy			110.10 ± 1217.71	154,474.64	24.88
	M	Total cost	717	33.82	519.69 ± 1229.52	372,619.35	100.00
		Scheme amount			432.81 ± 1213.72	20,645.56	83.28
		Patient levy			86.89 ± 153.49	62,297.63	16.72

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = percentage of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.2.2 Average cost per prescription for Rheumatoid Arthritis patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	**F**	Total cost	1,835	73.99	8241.22 ± 2722.71	15,122,642.28	100.00
			Scheme amount			7974.98 ± 2707.28	14,634,079.91	96.77
			Patient levy			266.25±1586.65	488562.37	3.23
		M	Total cost	645	26.01	8660.74 ± 2413.32	5,586,176.58	100.00
			Scheme amount			8273.76 ± 2696.28	5,336,573.48	95.53
			Patient levy			386.98 ± 1801.67	249603.1	4.47
	Other	**F**	Total cost	3,638	78.22	308.99 ± 395.07	1,124,103.67	100.00
			Scheme amount			250.30 ± 345.69	910,590.37	81.01
			Patient levy			58.69 ± 129.27	213,513.30	18.99
		M	Total cost	1,013	21.78	347.00 ± 439.83	351,507.45	100.00
			Scheme amount			276.97 ± 386.50	280,574.37	79.82
			Patient levy			70.02 ± 147.23	70,933.08	20.18

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = percentage of total number of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.3.1 Average cost per prescription for Rheumatoid Arthritis patient according to age

Phase	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	1	Total cost	118	1.88	164.06 ± 137.93	19,359.05	100.00
		Scheme amount			120.03±112.39	14,163.98	73.16
		Patient levy			44.03 ± 44.27	5,195.07	26.84
	2	Total cost	540	8.61	293.87 ± 339.23	158,690.67	100.00
		Scheme amount			257.62 ± 316.11	139,113.42	87.66
		Patient levy			36.25 ± 103.44	19,577.25	12.34
	3	Total cost	4,035	64.34	375.03 ± 398.04	1,513,263.24	100.00
		Scheme amount			310.22 ± 346.63	1,251,747.50	82.72
		Patient levy			64.81 ± 150.72	261,515.74	17.28
	4	Total cost	1,578	25.16	356.79 ± 351.98	563,017.48	100.00
		Scheme amount			271.51 ± 300.41	428,444.19	76.10
		Patient levy			85.28 ± 139.93	134,573.29	23.90
Phase 2	1	Total cost	155	2.17	3069.72 ± 3917.23	475,807.33	100.00
		Scheme amount			3056.04 ± 3927.38	473,686.50	99.55
		Patient levy			13.68 ± 26.91	2,120.83	0.45
	2	Total cost	1,010	14.16	3070.21 ± 4012.18	3,100,911.59	100.00
		Scheme amount			2776.19 ± 3774.94	2,803,955.16	90.42
		Patient levy			294.02 ± 1522.43	296,956.43	9.58
	3	Total cost	4,496	62.67	3159.17 ± 4162.54	14,118,352.00	100.00
		Scheme amount			3050.01 ± 4121.47	13,630,473.61	96.54
		Patient levy			109.17 ± 720.17	487,878.39	3.46
	4	Total cost	1,493	20.94	3006.94 ± 4236.33	4,489,359.06	100.00
		Scheme amount			2849.10 ± 4043.79	4,253,702.86	94.75
		Patient levy			157.84 ± 1267.10	235,656.20	5.25
Phase 3	1	Total cost	137	6.46	1373.92 ± 2883.71	188,226.72	100.00
		Scheme amount			1110.75 ± 2620.94	152,172.97	80.85
		Patient levy			263.17 ± 401.87	36,053.75	19.15
	2	Total cost	270	12.74	187.42 ± 264.59	50,604.74	100.00
		Scheme amount			141.85 ± 171.18	38,298.86	75.68
		Patient levy			45.58 ± 164.58	12,305.88	24.32
	3	Total cost	1,421	67.03	454.45 ± 1665.23	645,778.67	100.00
		Scheme amount			351.95 ± 1150.35	500,125.93	77.45
		Patient levy			102.50 ± 1203.87	145,652.74	22.55
	4	Total cost	292	13.77	373.03 ± 361.51	108,923.49	100.00
		Scheme amount			295.08 ± 336.97	86,163.59	79.10
		Patient levy			77.94 ± 119.69	22,759.90	20.90

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = percentage of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.3.2 Average cost per prescription for Rheumatoid Arthritis patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	61	2.46	7586.36 ± 2273.98	462,768.07	100.00
			Scheme amount			7586.36 ± 2273.98	462,768.07	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	379	15.28	7686.05 ± 2808.47	2,913,014.56	100.00
			Scheme amount			6954.71 ± 3116.91	2,635,834.00	90.48
			Patient levy			731.35 ± 2310.99	277,180.56	9.52
		3	Total cost	1,564	63.06	8433.73 ± 2514.17	13,190,351.27	100.00
			Scheme amount			8233.66 ± 2624.28	12,877,440.28	97.63
			Patient levy			200.07 ± 1198.37	312,910.99	2.37
		4	Total cost	476	19.19	8703.12 ± 2896.79	4,142,684.96	100.00
			Scheme amount			8392.04 ± 2446.70	3,994,611.04	96.43
			Patient levy			311.08 ± 2228.69	148,073.92	3.57
	Other	1	Total cost	94	2.02	138.72 ± 97.87	13,039.26	100.00
			Scheme amount			116.15 ± 86.50	10,918.43	83.74
			Patient levy			22.56 ± 31.56	2,120.83	16.26
		2	Total cost	632	13.59	297.31 ± 472.99	187,897.03	100.00
			Scheme amount			266.01 ± 425.57	168,121.16	89.48
			Patient levy			31.29 ± 119.28	19,775.87	10.52
		3	Total cost	2,907	62.50	319.23 ± 415.84	928,000.73	100.00
			Scheme amount			259.04 ± 364.19	753,033.33	81.15
			Patient levy			60.19 ± 134.81	174,967.40	18.85
		4	Total cost	1,018	21.89	340.54 ± 338.01	346,674.10	100.00
			Scheme amount			254.51 ± 287.43	259,091.82	74.74
			Patient levy			86.03 ± 138.83	87,582.28	25.26

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = percentage of total number of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.4.1 Average cost per prescription for Rheumatoid Arthritis patient according to prescriber

Phase	Prescriber	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	**1**	Total cost	2,461	39.24	310.83 ± 317.77	764,948.82	100.00
		Scheme amount			249.85 ± 277.16	614,873.38	80.83
		Patient levy			60.98 ± 118.69	150,075.44	19.62
	2	Total cost	125	1.99	644.58 ± 633.28	80,572.97	100.00
		Scheme amount			530.74 ± 527.27	66,342.45	82.34
		Patient levy			113.84 ± 169.53	14,230.52	17.66
	3	Total cost	1,446	23.06	316.68 ± 367.13	457,914.48	100.00
		Scheme amount			255.47 ± 330.28	369,410.27	80.67
		Patient levy			61.21 ± 138.57	88,504.21	19.33
	4	Total cost	2,229	35.54	423.55 ± 413.99	944,086.73	100.00
		Scheme amount			348.66 ± 357.37	777,169.46	82.32
		Patient levy			74.88 ± 168.20	166,917.27	17.68
	5	Total cost	10	0.16	680.74 ± 475.49	6,807.44	100.00
		Scheme amount			567.35 ± 410.80	5,673.53	83.34
		Patient levy			113.39 ± 82.23	1,133.91	16.66
Phase 2	**1**	Total cost	1,578	22.13	1146.61 ± 2723.64	1,809,347.24	100.00
		Scheme amount			1051.07 ± 2630.18	1,658,592.50	91.67
		Patient levy			95.54 ± 524.73	150,754.74	8.33
	2	Total cost	18	0.25	497.05 ± 403.89	8,946.91	100.00
		Scheme amount			303.18 ± 235.25	5,457.27	61.00
		Patient levy			193.87 ± 357.96	3,489.64	39.00
	3	Total cost	954	13.38	1117.29 ± 2515.89	1,065,898.39	100.00
		Scheme amount			1030.85 ± 2413.20	983,431.49	92.26
		Patient levy			86.44 ± 506.92	82,466.90	7.74
	4	Total cost	4,572	64.11	4216.81 ± 4414.89	19,279,275.36	100.00
		Scheme amount			4044.92 ± 4328.92	18,493,379.46	95.92
		Patient levy			171.89 ± 1164.24	785,895.90	4.08
	5	Total cost	9	0.13	2329.12 ± 4251.78	20,962.08	100.00
		Scheme amount			2328.60 ± 4252.07	20,957.41	99.98
		Patient levy			0.52 ± 1.56	4.67	0.02
Phase 3	**1**	Total cost	925	43.63	418.40 ± 1121.25	387,018.14	100.00
		Scheme amount			336.49 ± 1046.31	311,255.60	80.42
		Patient levy			81.91 ± 174.39	75,762.54	19.58
	2	Total cost	5	0.24	1355.07 ± 1291.64	6,775.35	100.00
		Scheme amount			1269.77 ± 1255.69	6,348.83	93.70
		Patient levy			85.30 ± 38.64	426.52	6.30
	3	Total cost	527	24.86	451.58 ± 2368.51	237,982.00	100.00
		Scheme amount			294.77 ± 1319.59	155,343.07	65.28
		Patient levy			156.81 ± 1970.07	82,638.93	34.72
	4	Total cost	622	29.34	378.79 ± 409.16	235,609.22	100.00
		Scheme amount			316.27 ± 384.66	196,722.53	83.50
		Patient levy			62.52 ± 102.86	38,886.69	16.50
	5	Total cost	38	1.79	2757.91 ± 3374.01	104,800.66	100.00
		Scheme amount			2260.91 ± 3131.83	859,14.54	81.98
		Patient levy			497.00 ± 544.50	18,886.12	18.02
		Total cost			7116.08 ± 11718.32	21,348.25	100.00

	6	Scheme amount	3	0.14	7058.93 ± 11769.37	21,176.78	99.20
		Patient levy			57.16 ± 95.04	171.47	0.80

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

% Rx = percentage of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.24.4.2 Average cost per prescription for Rheumatoid Arthritis patients during phase 2 according to prescriber

Phase	Medicines	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	**1**	Total cost	158	6.37	8897.15 ± 2560.87	1,405,750.01	100.00
			Scheme amount			8535.70 ± 2512.46	1,348,640.91	95.94
			Patient levy			361.45 ± 1593.48	57,109.10	4.06
		2	Total cost	0	-	-	-	0.00
			Scheme amount			-	-	0.00
			Patient levy			-	-	0.00
		3	Total cost	118	4.76	7227.97 ± 2830.68	852,900.86	100.00
			Scheme amount			6846.99 ± 2841.85	807,944.85	94.73
			Patient levy			380.98 ± 1370.57	44,956.01	5.27
		4	Total cost	2,202	88.79	8369.90 ± 2633.29	18,430,511.99	100.00
			Scheme amount			8081.02 ± 2697.37	17,794,411.63	96.55
			Patient levy			288.87 ± 1663.98	636,100.36	3.45
		5	Total cost	2	0.08	9828.00 ± 0.00	19,656.00	100.00
			Scheme amount			9828.00 ± 0.00	19,656.00	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
	Other	**1**	Total cost	1,420	30.53	284.22 ± 292.74	403,597.23	100.00
			Scheme amount			218.28 ± 240.98	309,951.59	76.80
			Patient levy			65.95 ± 127.71	93,645.64	23.20
		2	Total cost	18	0.39	497.05 ± 403.89	8,946.91	100.00
			Scheme amount			303.18 ± 235.25	5,457.27	61.00
			Patient levy			193.87 ± 357.96	3,489.64	39.00
		3	Total cost	836	17.97	254.78 ± 282.41	212,997.53	100.00
			Scheme amount			209.91 ± 244.41	175,486.64	82.39
			Patient levy			44.87 ± 126.81	37,510.89	17.61
		4	Total cost	2,370	50.96	358.13 ± 487.98	848,763.37	100.00
			Scheme amount			294.92 ± 433.73	698,967.83	82.85
			Patient levy			63.20 ± 135.45	149,795.54	17.65
		5	Total cost	7	0.15	186.58 ± 59.43	1,306.08	100.00
			Scheme amount			185.92 ± 59.73	1,301.41	99.64
			Patient levy			0.67 ± 1.77	4.67	0.36

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

% Rx = percentage of total number of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.25.1 Average number of medicine items per prescription for Rheumatoid Arthritis patient according to prescriber

Phase		Prescriber	Frequency (*n* = Rx)	Sum (Items)	Average items per Rx Mean ± SD
Phase 1		**1**	2,461	6,743.00	2.74 ± 2.23
		2	125	339.00	2,71 ± 2.08
		3	1,446	3,477.00	2.40 ± 2.17
		4	2,229	6,959.00	3.12 ± 2.45
		5	10	32.00	3.20 ± 1.75
Phase 2	***Biologics***	**1**	158	170.00	1.08 ± 0.37
		2	0	0.00	0.00 ± 0.00
		3	118	125.00	1.06 ± 0.24
		4	2,202	2,268.00	1.03 ± 0.19
		5	2	2.00	1.00 ± 0.00
	Others	**1**	1,420	3,647.00	2.57 ± 2.19
		2	18	94.00	5.22 ± 2.46
		3	836	1,870.00	2.24 ± 1.91
		4	2,370	6,822.00	2.88 ± 2.31
		5	7	13.00	1.86 ± 0.38
Phase 3		**1**	925	2,051.00	2.22 ± 1.78
		2	5	22.00	4.40 ± 2.51
		3	527	1,073.00	2.04 ± 1.68
		4	622	1,722.00	2.77 ± 1.96
		5	38	126.00	3.32 ± 2.87
		6	3	7.00	2.33 ± 0.58

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology; 6 = Clinical haemotology.

Frequency = number of prescriptions claimed per year.

Sum = number of items claimed per year.

Table A.26.1 Average number of prescriptions per Rheumatoid Arthritis patient

Phase	Number of patients	Number of prescriptions	Average Rx per patient Mean ± SD
Phase 2	141	2,480.00	17.59 ± 12.84

Table A.26.2 Average number of prescriptions per Rheumatoid Arthritis patient according to gender

Phase	Gender	Number of patients	Average Rx per patient Mean ± SD	Number of prescriptions
Phase 2	**F**	100	18.35 ± 13.53	1,835.00
	M	41	15.73 ± 10.92	645.00

Table A.26.3 Average number of prescriptions per Rheumatoid Arthritis patient according to age

Phase	Age group	Number of patients	Average Rx per patient Mean ± SD	Number of prescriptions
Phase 2	**1**	4	15.25 ± 17.63	61.00
	2	20	18.95 ± 16.15	379.00
	3	92	17.00 ± 11.49	1,564.00
	4	25	19.04 ± 14.48	476.00

Table A.27.1 Combinations prescribed during phase 1 of MS treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
CITALOPRAM	OXYBUTYNIN			21.00
AMILORIDE/HYDROCHLORT	ENALAPRIL			15.00
METFORMIN	ATORVASTATIN			13.00
INDAPAMIDE	LISINOPRIL			12.00
LOSARTAN	ASPIRIN			12.00
VALSARTAN/HTCZ	ESOMEPRAZOLE			11.00
ESCITALOPRAM	LAMOTRIGINE			10.00
OXYBUTYNIN	IMIPRAMINE			9.00
ATORVASTATIN	WARFARIN			8.00
ESCITALOPRAM	ETHINYL OESTRADIOL/GES			8.00
Combination of 3 items per prescription				
CALCIUM CARBONATE/MAGN	MELOXICAM	ALENDRONATE		12.00
CYPROTERONE	THYROXINE	CYPROTERONE/ETHI		10.00
INDOMETHACIN	OXYBUTYNIN	AMITRIPTYLINE		8.00
CALCIUM/MAGNESIUM	PANTOPRAZOLE	ALENDRONATE		6.00
ZOLPIDEM	AZATHIOPRINE	FLUOXETINE		6.00
ASPIRIN	FLUOXETINE	AMANTADINE		5.00
GABAPENTIN	AMITRIPTYLINE	SERTRALINE		5.00
CARVEDILOL	LISINOPRIL	LISINOPRIL/HTCZ		4.00
METHYLPREDNISOLONE ACE	CLOBETASONE	ARACHIS OIL/COAL TAR		4.00
SPIRONOLACTONE	MAGNESIUM L-ASPARTATE	POTASSIUM CHLORIDE		4.00
VALPROATE (SODIUM	OLANZAPINE	OLANZAPINE		4.00
Combination of 4 items per prescription				
THYROXINE	CARBIDOPA/LEVODOPA	UNKNOWN	AMITRIPTYLINE	14.00
ALPRAZOLAM	FLUOXETINE	INDAPAMIDE	LISINOPRIL	12.00
CARBIDOPA/LEVODOPA	THYROXINE	UNKNOWN	AMITRIPTYLINE	10.00
CARVEDILOL	AMLODIPINE	LISINOPRIL/HTCZ	LISINOPRIL	9.00
ASPIRIN	TRIAMCINOLONE	FLUOXETINE	AMANTADINE	8.00
ASPIRIN	DESLORATADINE	FLUOXETINE	AMANTADINE	6.00
CARVEDILOL	AMLODIPINE	LISINOPRIL	LISINOPRIL/HTCZ	5.00
PAROXETINE	OXYBUTYNIN	BACLOFEN	IBUPROFEN	4.00
BETAMETHASONE	CLOBETASONE	OESTRADIOL	PERINDOPRIL	3.00
ESOMEPRAZOLE	PREDNISONE ISONE	PREDNISONE ISONE	POTASSIUM Cl	3.00
THYROXINE	CARBIDOPA/LEVODOPA	UNKNOWN	AMITRIPTYLINE	
n = frequency with which specific combination was prescribed during four years				

Table 27.2.1 Combinations prescribed during phase 2 of MS treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
ESCITALOPRAM	BACLOFEN			38.00
TRAMADOL	AMITRIPTYLINE			22.00
OXYBUTYNIN	FLUOXETINE			19.00
FOLIC ACID	METHOTREXATE			17.00
FLUOXETINE	TOPIRAMATE			16.00
METFORMIN	ATORVASTATIN			16.00
THYROXINE	THYROXINE			13.00
BISOPROLOL	PERINDOPRIL			12.00
RISPERIDONE	SERTRALINE			12.00
SPIRONOLACTONE	POTASSIUM CHLORIDE			12.00
Combination of 3 items per prescription				
VALPROIC ACID	LAMOTRIGINE	CLONAZEPAM		46.00
SPIRONOLACTONE	THYROXINE	POTASSIUM CHLORIDE		18.00
OESTRADIOL	VENLAFAXINE	ZOLPIDEM		13.00
RISPERIDONE	OXCARBAZEPINE	SERTRALINE		12.00
CARBAMAZEPINE	PERINDOPRIL	TOPIRAMATE		8.00
PAROXETINE	ZOLPIDEM	TOPIRAMATE		8.00
SPIRONOLACTONE	MAGNESIUM L-ASPARTATE	POTASSIUM CHLORIDE		7.00
ENALAPRIL/HTCZ	RISPERIDONE	AMITRIPTYLINE		6.00
ESCITALOPRAM	BISOPROLOL	PERINDOPRIL		6.00
FLUVOXAMINE	RISPERIDONE	OXCARBAZEPINE		6.00
Combination of 4 items per prescription				
CARBIDOPA/LEVODOPA	THYROXINE	UNKNOWN	AMITRIPTYLINE	8.00
INDOMETHACIN	DULOXETINE HCl	METHYLPHENIDATE	FLUOXETINE	6.00
ESCITALOPRAM	BISOPROLOL	LANSOPRAZOLE	PERINDOPRIL	5.00
GABAPENTIN	ZOLPIDEM	AMITRIPTYLINE	SERTRALINE	5.00
ASPIRIN	ETILEFRINE HYDROCHLORI	THYROXINE	ETHINYL OESTRA	4.00
FLUVOXAMINE	RISPERIDONE	MONTELUKAST	OXCARBAZEPINE	4.00
VENLAFAXINE	THYROXINE	ETHINYL OESTRADIOl	ZOPICLONE	4.00
VENLAFAXINE	THYROXINE	ZOPICLONE	AMANTADINE	4.00
ALPRAZOLAM	INDAPAMIDE	LISINOPRIL	ETHINYL OESTRA	3.00
BACLOFEN	GABAPENTIN	GABAPENTIN	OXAZEPAM	3.00
BACLOFEN	OXYBUTYNIN	FLUOXETINE	CARBAMAZEPINE	3.00
CLOMIPRAMINE	PREDNISONE ISONE	CELECOXIB	LAMOTRIGINE	3.00
DICLOFENAC/MISOPROSTOL	LORAZEPAM	VENLAFAXINE	TEMAZEPAM	3.00
HYDROXYZINE	ZOPICLONE	PAR/DEXTRO/DIPHEN/	FLAVOXATE	3.00
IMIPRAMINE	GABAPENTIN	CONJ. OESTROGENS	CLONAZEPAM	3.00
THYROXINE	ZOPICLONE	AMANTADINE	VENLAFAXINE	3.00
n = frequency with which specific combination was prescribed during four years				

Table 27.2.2 Combinations of biologic immunomodulators prescribed during phase 2

MEDICINE ITEMS			n
1 biologic immunomodulator per prescription			
Interferon beta 1a			2386.00
Interferon beta 1b			1622.00
Combinations with 2 biologic immunomodulators per prescription			
Interferon beta 1a	Interferon beta 1a		31.00
Interferon beta 1b	Interferon beta 1b		9.00
Combinations with 3 biologic immunomodulators per prescription			
Interferon beta 1a	Interferon beta 1a	Interferon beta 1a	6.00
n = frequency with which specific combination was prescribed during four years			

Table 27.3 Combinations prescribed during phase 3 of MS treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
PAROXETINE	BACLOFEN			11.00
ASPIRIN	LOSARTAN/HTCZ			6.00
MIANSERIN	ESOMEPRAZOLE			6.00
PAR/DEXTRO/DIPHEN/CAFF	TRAMADOL/PAR			6.00
FLUCONAZOLE	CYPROTERONE/ETHI			5.00
FLUCONAZOLE	LEVOFLOXACIN			5.00
CONJUGATED OESTRO	AMANTADINE			4.00
CYPROTERONE ACET./ETHI	ZOLPIDEM			4.00
TRAMADOL	AMITRIPTYLINE			4.00
VALPROATE (SODIUM	VALPROATE (SODIUM			4.00
ZOLPIDEM	CITALOPRAM			4.00
Combination of 3 items per prescription				
PAROXETINE	BACLOFEN	IBUPROFEN		6.00
DULOXETINE HYDROCHLORI	TEMAZEPAM	OESTRADIOL/NORETHI		5.00
DULOXETINE HYDROCHLORI	MIANSERIN	OXCARBAZEPINE		4.00
MIANSERIN	MELOXICAM	OXCARBAZEPINE		4.00
IBUPROFEN	TOLTERADINE	POTASSIUM CHLORIDE		2.00
PAROXETINE	BACLOFEN	TROSPIUM		2.00
TELITHROMYCIN	MIZOLASTINE	NOSCAPINE		2.00
Combination of 4 items per prescription				
IBUPROFEN	TOLTERADINE	POTASSIUM CHLORIDE	FLUNITRAZEPAM	12.00
CALCIUM/MAGNESIUM	PROPRANOLOL	POTASSIUM CHLORIDE	ZOPICLONE	4.00
DULOXETINE HYDROCHLORI	MIANSERIN	OXCARBAZEPINE	OESTRADIOL/NOR	4.00
IBUPROFEN	TOLTERADINE	FLUNITRAZEPAM	POTASSIUM CHL	4.00
AZATHIOPRINE	BACLOFEN	METHYLPREDNISOLON	TRIMETHOPRIM/SU	2.00
DULOXETINE HYDROCHLORI	MIANSERIN	MELOXICAM	OXCARBAZEPINE	2.00
n = frequency with which specific combination was prescribed during four years				

Table A.28.1.1 Average cost per medicine item for Multiple Sclerosis patients

Phase	Variables	Frequency (n)	Mean ± SD	Total cost	%
Phase 1	Total cost	6,171	133.24 ± 146.80	822,220.75	100.00
	Scheme amount		108.73 ± 131.07	670,976.25	81.61
	Patient levy		24.51 ± 62.54	151,244.50	18.39
Phase 2	Total cost	14,321	2268.35 ± 3387.05	32,484,977.66	100.00
	Scheme amount		2192.07 ± 3370.81	31,392,633.45	96.64
	Patient levy		76.28 ± 543.67	1,092,344.21	3.36
Phase 3	Total cost	2,234	170.01 ± 206.92	379,800.98	100.00
	Scheme amount		135.64 ± 199.50	303,015.24	79.78
	Patient levy		34.37 ± 80.32	76,785.74	20.22

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.2.2 Average cost per medicine item for Multiple Sclerosis patients during phase 2

Phase	Medicines	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	Total cost	4,106	18.67	7531.06 ± 1047.72	30,922,520.07	100.00
		Scheme amount			7350.99 ± 1498.12	30,183,184.60	97.61
		Patient levy			180.06 ± 997.89	739,335.47	2.39
	Other	Total cost	10,215	71.33	152.96 ± 183.34	1,562,457.59	100.00
		Scheme amount			118.40 ± 168.84	1,209,448.85	77.41
		Patient levy			34.56 ± 90.07	353,008.74	22.59

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all the biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.2.1 Average cost per medicine item for Multiple Sclerosis patient according to gender

Phase	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	F	Total cost	5,307	86.00	26.23 ± 64.83	699,724.79	100.00
		Scheme amount			105.62 ± 129.71	560,533.43	80.11
		Patient levy			26.23 ± 64.83	139,191.36	19.89
	M	Total cost	864	14.00	13.95 ± 44.60	122,495.96	100.00
		Scheme amount			127.83 ± 137.63	110,442.82	90.16
		Patient levy			13.95 ± 44.60	12,053.14	9.84
Phase 2	F	Total cost	11,796	82.37	2211.32 ± 3364.53	26,084,733.95	100.00
		Scheme amount			2135.35 ± 3344.88	25,188,578.15	96.56
		Patient levy			75.97 ± 540.39	896,155.80	3.44
	M	Total cost	2,525	17.63	2534.75 ± 3478.66	6,400,243.71	100.00
		Scheme amount			2457.05 ± 3477.85	6,204,055.30	96.93
		Patient levy			77.70 ± 558.80	196,188.41	3.07
Phase 3	F	Total cost	2,088	93.46	33.06 ± 79.22	351,614.31	100.00
		Scheme amount			135.34 ± 196.99	282,581.95	80.37
		Patient levy			33.06 ± 79.22	69,032.36	19.63
	M	Total cost	146	6.54	53.11 ± 92.95	28,186.67	100.00
		Scheme amount			139.95 ± 233.21	20,433.29	72.49
		Patient levy			53.11 ± 92.95	7,753.38	27.51

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all medicine items claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.2.2 Average cost per medicine item for Multiple Sclerosis patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	F	Total cost	3,292	80.18	182.87 ± 1003.87	24,830,114.97	100.00
			Scheme amount			7359.69 ± 1469.92	24,228,102.88	97.58
			Patient levy			182.87 ± 1003.87	602,012.09	2.42
		M	Total cost	814	19.82	168.70 ± 973.88	6,092,405.10	100.00
			Scheme amount			7315.83 ± 1607.62	5,955,081.72	97.74
			Patient levy			168.70 ± 973.88	137,323.38	2.26
	Other	F	Total cost	8,504	83.25	34.59 ± 94.39	1,254,618.98	100.00
			Scheme amount			112.94 ± 161.12	960,475.27	76.56
			Patient levy			34.59 ± 94.39	294,143.71	23.44
		M	Total cost	1,711	16.75	34.40 ± 64.50	351,614.31	100.00
			Scheme amount			145.51 ± 200.76	248,973.58	70.81
			Patient levy			34.40 ± 64.50	58,865.03	29.19

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.3.1 Average cost per medicine item for Multiple Sclerosis patients according to age

Phase	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	1	Total cost	339	5.49	93.98 ± 98.43	31,858.52	100.00
		Scheme amount			75.26 ± 95.09	25,512.59	80.08
		Patient levy			18.72 ± 45.89	6,345.93	19.92
	2	Total cost	1,267	20.53	131.83 ± 159.86	167,034.67	100.00
		Scheme amount			112.08 ± 148.47	142,002.10	85.01
		Patient levy			19.76 ± 61.83	25,032.57	14.99
	3	Total cost	4,416	71.56	135.95 ± 146.00	600,367.12	100.00
		Scheme amount			109.05 ± 127.53	481,565.99	80.21
		Patient levy			26.90 ± 64.62	118,801.13	19.79
	4	Total cost	149	2.41	154.10 ± 132.38	22,960.44	100.00
		Scheme amount			146.95 ± 132.88	21,895.57	95.36
		Patient levy			7.15 ± 14.42	1,064.87	4.64
Phase 2	1	Total cost	708	4.94	2318.43 ± 3481.38	1,641,446.82	100.00
		Scheme amount			2277.39 ± 3495.08	1,612,390.69	98.23
		Patient levy			41.04 ± 208.85	29,056.13	1.77
	2	Total cost	2,463	17.20	3272.41 ± 3680.44	8,059,947.00	100.00
		Scheme amount			3154.85 ± 3671.60	7,770,400.82	96.41
		Patient levy			117.56 ± 715.33	289,546.18	3.59
	3	Total cost	10,504	73.35	2081.02 ± 3290.74	21,859,058.66	100.00
		Scheme amount			2009.14 ± 3274.38	21,104,041.70	96.55
		Patient levy			71.88 ± 526.82	755,016.96	3.45
	4	Total cost	646	4.51	1431.15 ± 2871.87	924,525.08	100.00
		Scheme amount			1402.17± 2848.06	905,800.24	97.97
		Patient levy			28.99 ± 177.33	18,724.84	2.03
Phase 3	1	Total cost	71	3.18	150.36 ± 93.22	10,675.68	100.00
		Scheme amount			119.13 ± 84.66	8,458.39	79.23
		Patient levy			31.23 ± 47.53	2,217.29	20.77
	2	Total cost	249	11.15	121.73 ± 139.66	30,310.23	100.00
		Scheme amount			90.24 ± 127.38	22,470.05	74.13
		Patient levy			31.49 ± 73.97	7,840.18	25.87
	3	Total cost	1,515	67.82	186.52 ± 235.09	282,581.81	100.00
		Scheme amount			152.27 ± 229.18	230,695.76	81.64
		Patient levy			34.25 ± 86.30	51,886.05	18.36
	4	Total cost	399	17.86	140.94 ± 113.48	56,233.26	100.00
		Scheme amount			103.74 ± 93.41	41,391.04	73.61
		Patient levy			37.20 ± 63.58	14,842.22	26.39

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all the items claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.3.2 Average cost per medicine item for Multiple Sclerosis patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	201	4.90	7804.62 ± 748.11	1,568,727.66	100.00
			Scheme amount			7775.37 ± 852.36	1,562,849.46	99.63
			Patient levy			29.24 ± 361.27	5,878.20	0.37
		2	Total cost	1,057	25.74	7437.83 ± 1051.86	7,861,783.45	100.00
			Scheme amount			7210.47 ± 1598.30	7,621,467.25	96.94
			Patient levy			227.36 ± 1073.90	240,316.20	3.06
		3	Total cost	2,736	66.63	7542.85 ± 1064.16	20,637,237.15	100.00
			Scheme amount			7366.86 ± 1501.88	20,155,717.53	97.67
			Patient levy			175.99 ± 1014.97	481,519.62	2.33
		4	Total cost	112	2.73	7631.89 ± 962.58	854,771.81	100.00
			Scheme amount			7528.13 ± 1121.95	843,150.36	98.64
			Patient levy			103.76 ± 410.18	11,621.45	1.36
	Other	1	Total cost	507	4.96	143.43 ± 131.32	72,719.16	100.00
			Scheme amount			97.71 ± 114.14	49,541.23	68.13
			Patient levy			45.72 ± 96.33	23,177.93	31.87
		2	Total cost	1,406	13.76	140.94 ± 195.86	198,163.65	100.00
			Scheme amount			105.93 ± 160.35	148,933.57	75.16
			Patient levy			35.01 ± 118.27	49,230.08	24.84
		3	Total cost	7,768	76.05	157.29 ± 187.36	1,221,821.51	100.00
			Scheme amount			122.08 ± 175.91	948,324.17	77.62
			Patient levy			35.21 ± 85.94	273,497.34	22.38
		4	Total cost	534	2.64	130.62 ± 117.79	69,753.27	100.00
			Scheme amount			117.32 ± 119.02	62,649.88	89.82
			Patient levy			13.30 ± 39.93	7,103.39	10.18

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.4.1 Average cost per medicine item for Multiple Sclerosis patients according to prescriber

Phase	Prescriber	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	1	Total cost	3,634	58.89	115.34 ± 126.01	419,142.95	100.00
		Scheme amount			95.45 ± 112.20	346,852.16	82.75
		Patient levy			19.89 ± 46.54	72,290.79	17.25
	2	Total cost	994	16.11	176.93 ± 183.70	175,872.45	100.00
		Scheme amount			150.74 ± 168.90	149,833.40	85.19
		Patient levy			26.20 ± 64.28	26,039.05	14.81
	3	Total cost	1,187	19.40	145.61 ± 165.53	172,844.83	100.00
		Scheme amount			105.52 ± 140.21	125,252.13	72.47
		Patient levy			40.09 ± 97.73	47,592.70	27.53
	4	Total cost	310	5.02	155.95 ± 130.10	48,345.57	100.00
		Scheme amount			142.78 ± 130.90	44,262.30	91.55
		Patient levy			13.17 ± 29.85	4,083.27	8.45
	5	Total cost	46	0.75	130.76 ± 118.52	6,014.95	100.00
		Scheme amount			103.83 ± 110.88	4,776.26	79.41
		Patient levy			26.93 ± 57.19	1,238.69	20.59
Phase 2	1	Total cost	5,001	34.92	422.33 ± 1492.96	2,112,056.39	100.00
		Scheme amount			392.46 ± 1494.89	1,962,700.65	92.93
		Patient levy			29.87 ± 97.09	149,355.74	7.07
	2	Total cost	6,787	47.39	4391.34 ± 3716.37	29,803,991.08	100.00
		Scheme amount			4267.45 ± 3735.77	28,963,213.90	97.18
		Patient levy			123.88 ± 780.17	840,777.18	2.82
	3	Total cost	1,920	13.41	225.40 ± 690.85	432,773.85	100.00
		Scheme amount			182.19 ± 686.76	349,809.23	80.83
		Patient levy			43.21 ± 107.97	82,964.62	19.17
	4	Total cost	563	3.93	235.11 ± 708.31	132,367.05	100.00
		Scheme amount			201.95 ± 710.37	113,699.17	85.90
		Patient levy			33.16 ± 73.91	18,667.88	14.10
	5	Total cost	50	0.35	75.79 ± 104.11	3,789.29	100.00
		Scheme amount			64.21 ± 90.06	3,210.50	84.73
		Patient levy			11.58 ± 48.84	578.79	15.27
Phase 3	1	Total cost	1,249	55.91	146.02 ± 167.51	182,379.80	100.00
		Scheme amount			110.48 ± 154.03	137,983.42	75.66
		Patient levy			35.55 ± 84.53	44,396.38	24.34
	2	Total cost	599	26.81	238.24 ± 291.06	142,703.13	100.00
		Scheme amount			207.25 ± 290.86	124,144.41	86.99
		Patient levy			30.98 ± 72.52	18,558.72	13.01
	3	Total cost	308	13.79	144.00 ± 131.99	44,352.83	100.00
		Scheme amount			107.46 ± 114.07	33,097.36	74.62
		Patient levy			36.54 ± 81.78	11,255.47	25.38
	4	Total cost	77	3.45	134.61 ± 98.74	10,365.22	100.00
		Scheme amount			101.17 ± 78.23	7,790.05	75.16
		Patient levy			33.44 ± 60.55	2,575.17	24.84

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

% items = % of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.28.4.2 Average cost per medicine item for Multiple Sclerosis patients during phase 2 according to prescriber

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	200	4.87	7640.53 ± 985.13	1,528,106.63	100.00
			Scheme amount			7606.72 ± 1114.35	1,521,344.43	99.56
			Patient levy			33.81 ± 335.66	6,762.20	0.44
		2	Total cost	3,887	94.67	7523.97 ± 1052.91	29,245,671.07	100.00
			Scheme amount			7335.50 ± 1517.36	28,513,097.80	97.50
			Patient levy			188.47 ± 1022.16	732,573.27	2.50
		3	Total cost	14	0.34	7928.62 ± 100.02	111,000.62	100.00
			Scheme amount			7928.62 ± 100.02	111,000.62	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		4	Total cost	5	0.12	7548.35 ± 0.00	37,741.75	100.00
			Scheme amount			7548.35 ± 0.00	37,741.75	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
	Other	1	Total cost	4,801	47.00	121.63 ± 142.15	583,949.76	100.00
			Scheme amount			91.93 ± 131.96	441,356.22	75.58
			Patient levy			29.70 ± 71.74	142,593.54	24.42
		2	Total cost	2,900	28.40	192.52 ± 223.32	558,320.01	100.00
			Scheme amount			155.21 ± 211.32	450,116.10	80.62
			Patient levy			37.31 ± 105.59	108,203.91	19.38
		3	Total cost	1,906	18.66	168.82 ± 203.53	321,773.23	100.00
			Scheme amount			125.29 ± 175.52	238,808.61	74.22
			Patient levy			43.53±108.30	82,964.62	25.78
		4	Total cost	558	5.46	169.58 ± 147.64	94,625.30	100.00
			Scheme amount			136.12 ± 142.64	75,957.42	91.55
			Patient levy			33.45 ± 74.18	18,667.88	8.45
		5	Total cost	50	0.50	75.79 ± 104.11	3,789.29	100.00
			Scheme amount			64.21 ± 90.06	3,210.50	84.73
			Patient levy			11.58 ± 48.84	578.79	15.27

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.1.1 Average cost per prescription for Multiple Sclerosis patients

Phase	Variables	Frequency	Mean ± SD	Total cost	%
Phase 1	Total cost	3,008	273.34 ± 320.81	822,220.75	100.00
	Scheme amount		223.06 ± 285.74	670,976.25	81.61
	Patient levy		50.28 ± 112.69	151,244.50	18.39
Phase 2	Total cost	8,986	3615.07 ± 3733.46	32,484,977.66	100.00
	Scheme amount		3493.50 ± 3742.93	31,392,633.45	96.64
	Patient levy		121.56 ± 696.65	1,092,344.21	3.36
Phase 3	Total cost	976	389.14 ± 498.34	379,800.98	100.00
	Scheme amount		310.47 ± 451.59	303,015.24	79.78
	Patient levy		78.67 ± 179.18	76,785.74	20.22

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.1.2 Average cost per prescription for Multiple Sclerosis patients during phase 2

Phase	Medicines	Variables	Frequency	% Rx	Mean ± SD	Total cost	%
Phase 2	*Biologics*	Total cost	4,053	45.10	7629 ± 1169.91	30,922,520.07	100.00
		Scheme amount			7447.12 ± 1565.43	30,183,184.60	97.61
		Patient levy			182.42 ± 1017.41	739,335.47	2.39
	Other	Total cost	4,933	54.90	316.74 ± 379.31	1,562,457.59	100.00
		Scheme amount			245.18 ± 331.53	1,209,448.85	77.41
		Patient levy			71.56 ± 167.82	353,008.74	22.59

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.2.1 Average cost per prescription for Multiple Sclerosis patients according to gender

Phase	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	F	Total cost	2,610	86.77	268.09 ± 300.07	699,724.79	100.00
		Scheme amount			214.76 ± 258.10	560,533.43	80.11
		Patient levy			53.33 ± 117.25	139,191.36	19.89
	M	Total cost	398	13.23	307.78 ± 431.76	122,495.96	100.00
		Scheme amount			277.49 ± 420.93	110,442.82	90.16
		Patient levy			30.28 ± 73.28	12,053.14	9.84
Phase 2	F	Total cost	7,348	18.77	3549.91 ± 3722.64	26,084,733.95	100.00
		Scheme amount			3427.95 ± 3731.77	2,518,8578.15	96.56
		Patient levy			121.96 ± 687.44	896,155.80	3.44
	M	Total cost	1,638	18.23	3907.35 ± 3768.92	6,400,243.71	100.00
		Scheme amount			3787.58 ± 3779.79	6,204,055.30	96.93
		Patient levy			119.77 ± 736.75	196,188.41	3.07
Phase 3	F	Total cost	881	90.27	399.11 ± 511.31	351,614.31	100.00
		Scheme amount			320.75 ± 462.42	282,581.95	80.37
		Patient levy			78.36 ± 183.33	69,032.36	19.63
	M	Total cost	95	9.73	296.70 ± 344.73	28,186.67	100.00
		Scheme amount			215.09 ± 321.28	20,433.29	72.49
		Patient levy			81.61 ± 135.49	7,753.38	27.51

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.2.2 Average cost per prescription for Multiple Sclerosis patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	*Biologics*	F	Total cost	3,258	80.38	7621.28 ± 1137.76	24,830,114.97	100.00
			Scheme amount			7436.50 ± 1551.77	24,228,102.88	97.58
			Patient levy			184.78 ± 1009.83	602,012.09	2.42
		M	Total cost	795	19.62	7663.40 ± 1293.55	6,092,405.10	100.00
			Scheme amount			7490.67 ± 1620.51	5,955,081.72	97.74
			Patient levy			172.73 ± 1048.52	137,323.38	2.26
	Other	F	Total cost	4,090	82.91	306.75 ± 375.17	1,254,618.98	100.00
			Scheme amount			234.84 ± 320.40	960,475.27	76.56
			Patient levy			71.92 ± 176.64	294,143.71	23.44
		M	Total cost	843	17.09	365.17 ± 395.43	307,838.61	100.00
			Scheme amount			295.34 ± 377.16	248,973.58	70.81
			Patient levy			69.83 ± 115.95	58,865.03	29.19

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.3.1 Average cost per prescription for Multiple Sclerosis patients according to age

Phase	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	1	Total cost	164	5.45	194.26 ± 173.89	31,858.52	100.00
		Scheme amount			155.56 ± 167.28	25,512.59	80.08
		Patient levy			38.69 ± 82.93	6,345.93	19.92
	2	Total cost	690	0.03	242.08 ± 255.65	167,034.67	100.00
		Scheme amount			205.80 ± 226.19	142,002.10	85.01
		Patient levy			36.28 ± 104.18	25,032.57	14.99
	3	Total cost	2,077	69.05	289.05 ± 348.37	600,367.12	100.00
		Scheme amount			231.86 ± 309.82	481,565.99	80.21
		Patient levy			57.20 ± 118.58	118,801.13	19.79
	4	Total cost	77	2.56	298.19 ± 264.46	22,960.44	100.00
		Scheme amount			284.36 ± 257.10	21,895.57	95.36
		Patient levy			13.83 ± 21.35	1,064.87	4.64
Phase 2	1	Total cost	445	4.95	3688.64 ± 3826.17	1,641,446.82	100.00
		Scheme amount			3623.35 ± 3866.33	1,612,390.69	98.23
		Patient levy			65.29 ± 279.07	29,056.13	1.77
	2	Total cost	1,710	19.03	4713.42 ± 3703.69	8,059,947.10	100.00
		Scheme amount			4544.09 ± 3727.01	7,770,400.82	96.41
		Patient levy			169.33 ± 888.74	289,546.28	3.59
	3	Total cost	6,507	72.41	3359.31 ± 3689.89	21,859,058.66	100.00
		Scheme amount			3243.28 ± 3699.47	21,104,041.70	96.55
		Patient levy			116.03 ± 673.33	755,016.96	3.45
	4	Total cost	316	3.52	2925.71 ± 3551.55	924,525.08	100.00
		Scheme amount			2866.46 ± 3534.54	905,800.24	97.97
		Patient levy			59.07 ± 258.19	18,724.84	2.03
Phase 3	1	Total cost	48	4.92	222.41 ± 163.24	10,675.68	100.00
		Scheme amount			176.22 ± 123.36	8,458.39	79.23
		Patient levy			46.19 ± 74.85	2,217.29	20.77
	2	Total cost	150	15.37	202.07 ± 245.67	30,310.23	100.00
		Scheme amount			149.80 ± 201.41	22,470.05	74.13
		Patient levy			52.27 ± 110.91	7,840.18	25.87
	3	Total cost	674	69.06	419.26 ± 547.88	282,581.81	100.00
		Scheme amount			342.28 ± 510.13	230,695.76	81.64
		Patient levy			76.98 ± 186.81	51,886.05	18.36
	4	Total cost	104	10.66	540.70 ± 443.86	56,233.26	100.00
		Scheme amount			397.99 ± 322.63	41,391.04	73.61
		Patient levy			142.71 ± 223.34	14,842.22	26.39

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.3.2 Average cost per prescription for Multiple Sclerosis patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency	% Rx	Mean ± SD	Total cost	%
Phase 2	Biologics	1	Total cost	199	4.91	7883.05 ± 868.81	1,568,727.66	100.00
			Scheme amount			7853.51 ± 963.33	1,562,849.46	99.63
			Patient levy			29.54 ± 363.08	5,878.20	0.37
		2	Total cost	1,035	25.54	7595.93 ± 1232.51	7,861,783.45	100.00
			Scheme amount			7363.74 ± 1656.31	7,621,467.25	96.94
			Patient levy			232.19 ± 1125.86	240,316.20	3.06
		3	Total cost	2,707	66.79	7623.66 ± 1170.72	20,637,237.15	100.00
			Scheme amount			7445.78 ± 1576.91	20,155,717.53	97.67
			Patient levy			177.88 ± 1022.83	481,519.62	2.33
		4	Total cost	112	2.76	7631.89 ± 962.58	854,771.81	100.00
			Scheme amount			7528.13 ± 1121.95	843,150.36	98.64
			Patient levy			103.76 ± 410.18	11,621.45	1.36
	Other	1	Total cost	246	4.99	295.61 ± 266.21	72,719.16	100.00
			Scheme amount			201.39 ± 219.44	49,541.23	68.13
			Patient levy			94.22 ± 182.62	23,177.93	31.87
		2	Total cost	675	13.68	293.58 ± 358.10	198,163.65	100.00
			Scheme amount			220.64 ± 289.52	148,933.57	75.16
			Patient levy			72.93 ± 206.93	49,230.08	24.84
		3	Total cost	3,800	77.03	320.94 ± 389.49	1,221,821.51	100.00
			Scheme amount			249.10 ± 342.64	948,324.17	77.62
			Patient levy			71.84 ± 161.63	273,497.34	22.38
		4	Total cost	204	4.14	340.26 ± 368.96	69,753.27	100.00
			Scheme amount			305.61 ± 352.05	62,649.88	89.82
			Patient levy			34.65 ± 100.11	7,103.39	10.18

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.4.1 Average cost per prescription for Multiple Sclerosis patients according to prescriber

Phase	Prescriber	Variables	Frequency	% Rx	Mean ± SD	Total cost	%
Phase 1	1	Total cost	1,643	54.62	255.11 ± 324.66	419,142.95	100.00
		Scheme amount			211.11 ± 293.10	346,852.16	82.75
		Patient levy			44.00 ± 92.49	72,290.79	17.25
	2	Total cost	505	16.79	348.26 ± 309.03	175,872.45	100.00
		Scheme amount			296.70 ± 280.10	149,833.40	85.19
		Patient levy			51.56 ± 102.38	26,039.05	14.81
	3	Total cost	696	23.14	248.34 ± 305.04	172,844.83	100.00
		Scheme amount			179.96 ± 240.70	125,252.13	72.47
		Patient levy			68.38 ±161.09	47,592.70	27.53
	4	Total cost	127	4.22	380.67 ± 369.70	48,345.57	100.00
		Scheme amount			348.52 ± 373.31	44,262.30	91.55
		Patient levy			32.15 ± 48.97	4,083.27	8.45
	5	Total cost	37	1.23	162.57 ± 134.29	6,014.95	100.00
		Scheme amount			129.09 ± 116.11	4,776.26	79.41
		Patient levy			33.48 ± 69.31	1,238.69	20.59
Phase 2	1	Total cost	2,417	26.90	873.83 ± 2099.74	2,112,056.39	100.00
		Scheme amount			812.04 ± 2109.15	1,962,700.65	92.93
		Patient levy			61.79 ± 162.12	149,355.74	7.07
	2	Total cost	5,238	58.29	5689.96 ± 3358.04	29,803,991.08	100.00
		Scheme amount			5529.44 ± 3431.30	28,963,213.90	97.18
		Patient levy			160.51 ± 898.60	840,777.18	2.82
	3	Total cost	1,049	11.67	412.56 ± 980.62	432,773.85	100.00
		Scheme amount			333.47 ± 951.63	349,809.23	80.83
		Patient levy			79.09 ± 199.88	82,964.62	19.17
	4	Total cost	249	2.77	531.59 ± 1065.68	132,367.05	100.00
		Scheme amount			456.62 ± 1055.49	113,699.17	85.90
		Patient levy			74.97 ± 167.83	18,667.88	14.10
	5	Total cost	33	0.37	114.83 ± 151.45	3,789.29	100.00
		Scheme amount			97.29 ± 134.76	3,210.50	84.73
		Patient levy			17.54 ± 60.61	578.79	15.27
Phase 3	1	Total cost	493	50.51	369.94 ± 391.96	182,379.80	100.00
		Scheme amount			279.89 ± 364.43	137,983.42	75.66
		Patient levy			90.05 ± 173.52	44,396.38	24.34
	2	Total cost	276	28.28	517.04 ± 704.88	142,703.13	100.00
		Scheme amount			449.80 ± 643.99	124,144.41	86.99
		Patient levy			67.24 ± 164.09	18,558.72	13.01
	3	Total cost	173	17.73	256.37 ± 325.43	44,352.83	100.00
		Scheme amount			191.31 ± 229.89	33,097.36	74.62
		Patient levy			65.06 ± 213.35	11,255.47	25.38
	4	Total cost	33	3.38	314.10 ± 336.17	10,365.22	100.00
		Scheme amount			236.06 ± 237.21	7,790.05	75.16
		Patient levy			78.04 ± 186.89	2,575.17	24.84

	5	Total cost	1	0.10	0.00 ± 0.00	0.00	0.00
		Scheme amount			0.00 ± 0.00	0.00	0.00
		Patient levy			0.00 ± 0.00	0.00	0.00

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

% Rx = % of total number of prescriptions claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.29.4.2 Average cost per prescription for Multiple Sclerosis patients during phase 2 according to prescriber

Phase	Medicines	Age group	Variables	Frequency	% Rx	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	198	4.89	7717.71 ± 1291.34	1,528,106.63	100.00
			Scheme amount			7683.56 ± 1394.73	1,521,344.43	99.56
			Patient levy			34.15 ± 337.34	6,762.20	0.44
		2	Total cost	3,836	94.65	7624.00 ± 1166.05	29,245,671.07	100.00
			Scheme amount			7433.03 ± 1576.49	28,513,097.80	97.50
			Patient levy			190.97 ± 1042.35	732,573.27	2.50
		3	Total cost	14	0.35	7928.62 ± 100.02	111,000.62	100.00
			Scheme amount			7928.62 ± 100.02	111,000.62	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		4	Total cost	5	0.12	7548.35 ± 0.00	37,741.75	100.00
			Scheme amount			7548.35 ± 0.00	37,741.75	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
	Other	1	Total cost	2,219	44.98	263.16 ± 316.27	583,949.76	100.00
			Scheme amount			198.90 ± 285.74	441,356.22	75.58
			Patient levy			64.26 ± 135.82	142,593.54	24.42
		2	Total cost	1,402	28.42	398.23 ± 407.13	558,320.01	100.00
			Scheme amount			321.05 ± 373.57	450,116.10	80.62
			Patient levy			77.18 ± 186.63	108,203.91	19.38
		3	Total cost	1,035	20.98	310.89 ± 446.41	321,773.23	100.00
			Scheme amount			230.73 ± 355.13	238,808.61	74.22
			Patient levy			80.16 ± 201.01	82,964.62	25.78
		4	Total cost	244	4.95	387.81 ± 353.86	94,625.30	100.00
			Scheme amount			311.30 ± 284.50	75,957.42	91.55
			Patient levy			76.51 ± 169.20	18,667.88	8.45
		5	Total cost	33	0.66	114.83 ± 151.45	3,789.29	100.00
			Scheme amount			97.29 ± 134.76	3,210.50	84.73
			Patient levy			17.54 ± 60.61	578.79	15.27

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.30 Average number of medicine items per prescription for Multiple Sclerosis patients according to prescriber

Phase		Prescriber	Frequency (*n* = Rx)	Sum (Items)	Average items per Rx Mean ± SD
Phase 1		1	1,643	3,634.00	2.21 ± 1.67
		2	505	994.00	1.97 ± 1.29
		3	696	1,187.00	1.71 ± 1.04
		4	127	310.00	2.44 ± 1.97
		5	37	46.00	1.24 ± 0.55
Phase 2	*Biologics*	1	198	200.00	1.01 ± 0.10
		2	3,836	3,887.00	1.01 ± 0.13
		3	14	14.00	1.00 ± 0.00
		4	5	5.00	1.00 ± 0.00
		5	0	0.00	0.00 ± 0.00
	Other	1	2,219	4,801.00	2.16 ± 1.58
		2	1,402	2,900.00	2.07 ± 1.53
		3	1,035	1,906.00	1.84 ± 1.48
		4	244	558.00	2.29 ± 1.95
		5	33	50.00	1.52 ± 0.71
Phase 3		1	493	1,249.00	2.53 ± 1.92
		2	276	599.00	2.17 ± 2.18
		3	173	308.00	1.78 ± 1.32
		4	33	77.00	2.33 ± 2.01
		5	1	1.00	1.00 ± 0.00

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

Frequency = number of prescriptions claimed per year.

Sum = number of items claimed per year.

SD = Standard Deviation.

Table A.31.1 Average number of prescriptions per Multiple Sclerosis patient

Phase	Frequency (Patients)	Average Rx per patient Mean ± SD	Sum (Rx)
Phase 2	172	23.56 ± 14.82	4,053.00

Table A.31.2 Average number of prescriptions per Multiple Sclerosis patient according to gender

Phase	Gender	Frequency (Patients)	Average Rx per patient Mean ± SD	Sum (Rx)
Phase 2	**F**	143	22.78 ± 14.27	3,258.00
	M	29	27.41 ± 17.04	795.00

Table A.31.3 Average number of prescriptions per Multiple Sclerosis patient according to age

Phase	Age group	Frequency (Patients)	Average Rx per patient Mean ± SD	Sum (Rx)
Phase 2	**1**	11	18.09 ± 9.51	199.00
	2	50	20.70 ± 14.26	1,035.00
	3	106	25.54 ± 15.26	2,707.00
	4	5	22.40 ± 16.33	112.00

Table A.32.1 Combinations prescribed during phase 1 of Crohn's disease treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
Mesalazine	Pantoprazole			37.00
Azathioprine	Prednisolone			10.00
Meloxicam	Sulphasalazine			7.00
Azathioprine	Mesalazine			5.00
Azathioprine	Olsalazine			2.00
Folic acid	Methotrexate			2.00
Mebevirine	Sterculia			2.00
Prednisolone	Pantoprazole			2.00
Combination of 3 items per prescription				
Azathioprine	Mebeverine	Sterculia		2.00
Combination of 4 items per prescription				
Celecoxib	Perindopril	Bezafibrate	Atenolol	15.00
n = frequency with which specific combination was prescribed during four years				

MEDICINE ITEMS				n
Combination of 2 items per prescription				
Mesalazine	Pantoprazole			37.00
Azathioprine	Prednisolone			10.00
Meloxicam	Sulphasalazine			7.00
Azathioprine	Mesalazine			5.00
Azathioprine	Olsalazine			2.00
Folic acid	Methotrexate			2.00
Mebevirine	Sterculia			2.00
Prednisolone	Pantoprazole			2.00
Combination of 3 items per prescription				
Azathioprine	Mebeverine	Sterculia		2.00
Combination of 4 items per prescription				
Celecoxib	Perindopril	Bezafibrate	Atenolol	15.00
n = frequency with which specific combination was prescribed during four years				

Table A.32.2.1 Combinations prescribed during phase 2 of Crohn's disease treatment

MEDICINE ITEMS				n
Combination of 2 items per prescription				
Thyroxine	Alendronate			9.00
Diclofenac/Misoprostol	Diazepam			5.00
Indomethacin	Prednisolone			4.00
Combination of 3 items per prescription				
Calcium supplement	Thyroxine	Alendronate		3.00
Calcium supplement	Thyroxine	Diclofenac		2.00
Indomethacin	Prednisolone	Lanzoprazole		2.00
n = frequency with which specific combination was prescribed during four years				

Table A.32.2.2 Combinations of biologic immunomodulators prescribed during phase 2

MEDICINE ITEMS		n
1 biologic immunomodulator per prescription		
Etanercept		57.00
Adalimumab		48.00
Infliximab		17.00
Combinations with 2 biologic immunomodulators per prescription		
Infliximab	Infliximab	2.00
Etanercept	Etanercept	1.00
n = frequency with which specific combination was prescribed during four years		

Table 32.3 Combinations prescribed during phase 2 of Crohn's disease treatment

MEDICINE ITEMS			n
Combination of 2 items per prescription			
Perindopril	Azathioprine		6.00
Azathioprine	Sulphasalazine		3.00
Cirpofloxacin	Azathioprine		2.00
Combination of 3 items per prescription			
Azathioprine	Celecoxib	Sulphasalazine	6.00
Mesalazine	Azathioprine	Thyroxine	4.00
Celecoxib	Ciprofloxacin	Azathioprine	2.00
Desloratadine	Meloxicam	Chlorpheniramine/Pheny	2.00
n = frequency with which specific combination was prescribed during four years			

Table A.33.1.1 Average cost per medicine item for Crohn's disease patients

Phase	Variables	Frequency (n)	Mean ± SD	Total cost	%
Phase 1	Total cost	575	188.68 ± 166.19	108,489.52	100.00
	Scheme amount		181.12 ± 164.56	104,144.17	95.99
	Patient levy		7.56 ± 19.32	4,345.35	4.01
Phase 2	Total cost	384	2986.76 ± 5319.79	1,146,914.34	100.00
	Scheme amount		2910.36 ± 5332.84	1,117,576.68	97.44
	Patient levy		76.40 ± 541.07	29,337.66	2.56
Phase 3	Total cost	301	170.00 ± 184.12	51,169.41	100.00
	Scheme amount		157.06 ± 182.66	47,276.43	92.39
	Patient levy		12.93 ± 38.92	3,892.98	7.61

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.1.2 Average cost per medicine item for Crohn's disease patients during phase 2

Phase	Medicines	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	***Biologics***	Total cost	128	33.33	8660.69 ± 6052.28	1,108,568.02	100.00
		Scheme amount			8474.23 ± 6238.94	1,084,700.96	97.85
		Patient levy			186.46 ± 926.65	23,867.06	2.15
	Other	Total cost	256	66.67	149.79 ± 150.54	38,346.32	100.00
		Scheme amount			128.42 ± 142.13	32,875.72	85.73
		Patient levy			21.37 ± 54.14	5,470.60	14.27

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all the biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.2.1 Average cost per medicine item for Crohn's disease patients according to gender

Phase	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	F	Total cost	195	33.91	173.81 ± 162.25	33,892.77	100.00
		Scheme amount			160.90 ± 159.69	31,375.82	92.57
		Patient levy			12.91 ± 25.24	2,516.95	7.43
	M	Total cost	380	66.09	196.31 ± 167.88	74,596.75	100.00
		Scheme amount			191.50 ± 166.26	72,768.35	97.55
		Patient levy			4.81 ± 14.73	1,828.40	2.45
Phase 2	F	Total cost	283	73.70	3006.90 ± 5632.12	850,953.03	100.00
		Scheme amount			2919.78 ± 5647.77	826,298.72	97.10
		Patient levy			87.12 ± 571.63	24,654.31	2.90
	M	Total cost	101	26.30	2930.31 ± 4351.15	295,961.31	100.00
		Scheme amount			2883.94 ± 4355.55	291,277.96	98.42
		Patient levy			46.37 ± 445.59	4,683.35	1.58
Phase 3	F	Total cost	66	21.93	243.17 ± 308.10	16,049.18	100.00
		Scheme amount			223.77 ± 309.19	14,768.69	92.02
		Patient levy			19.40 ± 40.38	1,280.49	7.98
	M	Total cost	235	78.07	149.45 ± 123.12	35,120.23	100.00
		Scheme amount			138.33 ± 120.89	32,507.74	92.56
		Patient levy			11.12 ± 38.39	2,612.49	7.44

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all medicine items claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.2.2 Average cost per medicine item for Crohn's disease patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	F	Total cost	93	72.66	8814.61 ± 6811.03	819,758.79	100.00
			Scheme amount			8606.25 ± 7002.49	800,381.15	97.64
			Patient levy			208.36 ± 985.77	19,377.64	2.36
		M	Total cost	35	27.34	8251.69 ± 3325.82	288,809.23	100.00
			Scheme amount			8123.42 ± 3540.78	284,319.81	98.45
			Patient levy			128.27 ± 757.11	4,489.42	1.55
	Other	F	Total cost	190	74.22	164.18 ± 164.86	31,194.24	100.00
			Scheme amount			136.41 ± 156.61	25,917.57	83.08
			Patient levy			27.77 ± 61.34	5,276.67	16.92
		M	Total cost	66	25.78	108.36 ± 86.75	7,152.08	100.00
			Scheme amount			105.43 ± 84.90	6,958.15	97.29
			Patient levy			2.94 ± 9.68	193.93	2.71

F = Female; M = Male.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all the biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.3.1 Average cost per medicine item for Crohn's disease patients according to age

Phase	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	1	Total cost	164	28.52	242.35 ± 205.86	39,744.91	100.00
		Scheme amount			235.90 ± 201.19	38,687.45	97.34
		Patient levy			6.45 ± 14.48	1,057.46	2.66
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	377	6.43	172.79 ± 143.40	65,142.69	100.00
		Scheme amount			166.44 ± 143.79	62,747.26	96.32
		Patient levy			6.35 ± 17.21	2,395.43	3.68
	4	Total cost	34	5.91	105.94 ± 112.07	3,601.92	100.00
		Scheme amount			79.69 ± 87.01	2,709.46	75.22
		Patient levy			26.25 ± 41.26	892.46	24.78
Phase 2	1	Total cost	42	10.94	5460.82 ± 4200.31	229,354.63	100.00
		Scheme amount			5460.82 ± 4200.31	229,354.63	10.00
		Patient levy			0.00 ± 0.00	0.00	0.00
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	252	65.63	3480.95 ± 6005.57	877,181.02	100.00
		Scheme amount			3373.15 ± 6027.85	850,033.57	96.92
		Patient levy			107.80 ± 665.74	27,165.45	3.08
	4	Total cost	90	23.44	448.45 ± 1358.39	40,360.69	100.00
		Scheme amount			424.32 ± 1363.18	38,188.48±	94.62
		Patient levy			24.14 ± 39.83	2,172.21	5.38
Phase 3	1	Total cost	42	13.95	101.36 ± 153.76	4,257.07	100.00
		Scheme amount			60.72 ± 123.14	2,550.39	59.91
		Patient levy			40.64 ± 80.12	1,706.68	40.09
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	220	73.09	185.37 ± 191.61	40,780.71	100.00
		Scheme amount			181.18 ± 192.47	39,859.21	97.74
		Patient levy			4.19 ± 13.13	921.50	2.26
	4	Total cost	39	12.96	157.22 ± 154.17	6,131.63	100.00
		Scheme amount			124.79 ± 137.30	4,866.83	79.37
		Patient levy			32.43 ± 48.55	1,264.80	20.63

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.Total costs = average cost per medicine item.

% items = % of all medicine items claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.3.2 Average cost per medicine item for Crohn's disease patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	26	20.31	8510.59 ± 1881.93	221,275.39	100.00
			Scheme amount			8510.59 ± 1881.93	221,275.39	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	97	75.78	8838.39 ± 6864.97	857,323.43	100.00
			Scheme amount			8582.49 ± 6944.50	833,456.37	97.22
			Patient levy			193.78 ± 951.78	23,867.06	2.78
		4	Total cost	5	3.91	5,993.84 ± 0.00	29,969.20	100.00
			Scheme amount			5,993.84 ± 0.00	29,969.20	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
	Other	1	Total cost	16	6.25	504.95 ± 22.25	8,079.24	100.00
			Scheme amount			504.95 ± 22.25	8,079.24	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	155	60.55	128.23 ± 116.69	19,857.59	100.00
			Scheme amount			106.95 ± 100.49	16,577.20	83.48
			Patient levy			21.28 ± 62.45	3,298.39	16.52
		4	Total cost	85	33.20	122.25 ± 134.50	10,391.49	100.00
			Scheme amount			96.70 ± 117.69	8,219.28	79.10
			Patient levy			25.56 ± 40.55	2,172.21	20.90

Age group 1 = < 25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of medicine items claimed per year.

SD = Standard Deviation.

% items = % of all the biologics and "other" respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.4.1 Average cost per medicine item for Crohn's disease patients according to prescriber

Phase	Prescriber	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 1	**1**	Total cost	225	39.13	153.25 ± 129.22	34,480.22	100.00
		Scheme amount			144.58 ± 126.27	32,531.15	94.35
		Patient levy			8.66 ± 16.30	1,949.07	5.65
	3	Total cost	147	25.57	239.91 ± 204.61	35,267.02	100.00
		Scheme amount			237.28 ± 205.88	34,880.20	98.90
		Patient levy			2.63 ± 17.57	386.82	1.10
	4	Total cost	203	35.30	190.85 ± 162.47	38,742.28	100.00
		Scheme amount			180.95 ± 157.65	36,732.82	94.81
		Patient levy			9.90 ± 22.78	2,009.46	5.19
	5	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
Phase 2	**1**	Total cost	96	25.00	1491.95 ± 7730.98	143,227.48	100.00
		Scheme amount			1475.02 ± 7733.83	141,602.38	98.87
		Patient levy			16.93 ± 35.59	1,625.10	1.13
	3	Total cost	65	16.93	3886.49 ± 4002.85	252,621.60	100.00
		Scheme amount			3885.35 ± 4003.91	252,547.90	99.97
		Patient levy			1.13 ± 6.74	73.70	0.03
	4	Total cost	223	58.07	3368.01 ± 4156.83	751,065.26	100.00
		Scheme amount			3244.06 ± 4191.19	723,426.40	96.32
		Patient levy			123.94 ± 706.44	27,638.86	3.68
	5	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
Phase 3	**1**	Total cost	144	47.84	207.58 ± 218.00	29,891.70	100.00
		Scheme amount			203.54 ± 219.39	29,310.13	98.05
		Patient levy			4.04 ± 11.16	581.57	1.95
	3	Total cost	54	17.94	95.75 ± 118.67	5,170.69	100.00
		Scheme amount			85.72 ± 115.14	4,628.70	89.552
		Patient levy			10.04 ± 20.58	541.99	10.48
	4	Total cost	103	34.22	156.38 ± 143.73	16,107.02	100.00
		Scheme amount			129.49 ± 131.34	13,337.60	82.81
		Patient levy			26.89 ± 61.22	2,769.42	17.19
	5	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

% items = % of all medicine items claimed during each phase.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.33.4.2 Average cost per medicine item for Crohn's disease patients during phase 2 according to prescriber

Phase	Medicines	Age group	Variables	Frequency (n)	% items	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	3	2.64	44306.79 ± 0.02	13,2920.36	100.00
			Scheme amount			44306.79 ± 0.02	13,2920.36	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	30	23.44	8116.68 ± 965.59	243,500.43	100.00
			Scheme amount			8116.68 ± 965.59	243,500.43	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		4	Total cost	95	74.22	7706.81 ± 2763.24	732,147.23	100.00
			Scheme amount			7455.58 ± 3199.12	708,280.17	96.74
			Patient levy			251.23 ± 1069.44	23,867.06	3.26
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
	Other	1	Total cost	93	36.33	110.83 ± 116.27	10,307.12	100.00
			Scheme amount			93.36 ± 101.02	8,682.02	84.23
			Patient levy			17.47 ± 36.03	1,625.10	15.77
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	35	13.67	260.60 ± 205.62	9,121.17	100.00
			Scheme amount			258.50 ± 206.37	9,047.47	99.19
			Patient levy			2.11 ± 9.13	73.70	0.81
		4	Total cost	128	50.00	147.80 ± 141.03	18,918.03	100.00
			Scheme amount			118.33 ± 126.89	15,146.23	80.06
			Patient levy			29.47 ± 68.88	3771.80	19.94
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

Frequency = number of medicine claimed per year.

SD = Standard Deviation.

% items = % of total number of biologics and "other" items respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.34.1.1 Average cost per prescription for Crohn's disease patients

Phase	Variables	Frequency (n)	Mean ± SD	Total cost	%
Phase 1	Total cost	305	355.70 ± 263.70	108,489.52	100.00
	Scheme amount		341.46 ± 253.58	104,144.17	95.99
	Patient levy		14.25 ± 32.22	4,345.35	4.01
Phase 2	Total cost	260	4411.21 ± 7160.48	1,146,914.34	100.00
	Scheme amount		4298.37 ± 7195.86	1,117,576.68	97.44
	Patient levy		112.84 ± 656.15	29,337.66	2.56
Phase 3	Total cost	140	365.50 ± 352.74	51,169.41	100.00
	Scheme amount		337.69 ± 343.34	47,276.43	92.39
	Patient levy		27.81 ± 66.54	3,892.98	7.61

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.1.2 Average cost per prescription for Crohn's disease patients during phase 2

Phase	Medicines	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	Total cost	125	48.08	8868.54 ± 8272.23	1,108,568.02	100.00
		Scheme amount			8677.61 ± 8417.76	1,084,700.96	97.85
		Patient levy			190.94 ± 937.34	23,867.06	2.15
	Other	Total cost	135	51.92	284.05 ± 290.33	38,346.32	100.00
		Scheme amount			243.52 ± 241.23	32,875.72	85.73
		Patient levy			40.52 ± 90.28	5,470.60	14.27

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.2.1 Average cost per prescription for Crohn's disease patients according to gender

Phase	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	**F**	Total cost	85	24.87	398.74 ± 296.94	33,892.77	100.00
		Scheme amount			369.13 ± 272.01	31,375.82	92.57
		Patient levy			29.61 ± 48.54	2,516.95	7.43
	M	Total cost	220	75.13	339.08 ± 248.42	74,596.75	100.00
		Scheme amount			330.77 ± 245.90	72,768.35	97.55
		Patient levy			8.31 ± 20.25	1,828.40	2.45
Phase 2	**F**	Total cost	186	71.54	4575.02 ± 7932.25	850,953.03	100.00
		Scheme amount			4442.47 ± 7973.64	826,298.72	97.10
		Patient levy			132.55 ± 703.19	24,654.31	2.90
	M	Total cost	74	28.46	3999.48 ± 4713.33	295,961.31	100.00
		Scheme amount			3936.19 ± 4733.25	291,277.96	98.42
		Patient levy			63.29 ± 520.48	4,683.35	1.58
Phase 3	**F**	Total cost	27	19.29	594.41 ± 557.89	16,049.18	100.00
		Scheme amount			546.99 ± 537.13	14,768.69	92.02
		Patient levy			47.43 ± 81.71	1,280.49	7.98
	M	Total cost	113	80.71	310.80 ± 257.90	35,120.23	100.00
		Scheme amount			287.68 ± 257.37	32,507.74	92.56
		Patient levy			23.12 ± 61.88	2,612.49	7.44

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of all Rx claimed during each phase.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.2.2 Average cost per prescription for Crohn's disease patients during phase 2 according to gender

Phase	Medicines	Gender	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	**F**	Total cost	91	72.80	9008.34 ± 9503.46	819,758.79	100.00
			Scheme amount			8795.40 ± 9648.92	800,381.15	97.64
			Patient levy			212.94 ± 996.17	19,377.64	2.36
		M	Total cost	34	27.20	8494.39 ± 3258.30	288,809.23	100.00
			Scheme amount			8362.35 ± 3493.24	284,319.81	98.45
			Patient levy			132.04 ± 768.16	4,489.42	1.55
	Other	**F**	Total cost	95	70.37	328.36 ± 328.18	31,194.24	100.00
			Scheme amount			272.82 ± 273.17	25,917.57	83.08
			Patient levy			55.54 ± 103.86	5,276.67	16.92
		M	Total cost	40	29.63	178.80 ± 117.84	7,152.08	100.00
			Scheme amount			173.95 ± 114.11	6,958.15	97.29
			Patient levy			4.85 ± 12.24	193.93	2.71

F = Female; M = male.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.3.1 Average cost per prescription for Crohn's disease patients according to age

Phase	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	1	Total cost	113	37.05	351.72 ± 254.58	39,744.91	100.00
		Scheme amount			342.37 ± 244.99	38,687.45	97.34
		Patient levy			9.36 ± 19.27	1,057.46	2.66
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	178	58.36	365.97 ± 262.87	65,142.69	100.00
		Scheme amount			352.51 ± 256.27	62,747.26	96.32
		Patient levy			13.46 ± 29.05	2,395.43	3.68
	4	Total cost	14	4.59	257.28 ± 339.06	3,601.92	100.00
		Scheme amount			193.53 ± 259.13	2,709.46	75.22
		Patient levy			63.75 ± 81.99	892.46	24.78
Phase 2	1	Total cost	41	15.77	5594.02 ± 4292.90	229,354.63	100.00
		Scheme amount			5594.02 ± 4292.90	229,354.63	100.00
		Patient levy			0.00 ± 0.00	0.00	0.00
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	186	71.54	4716.12 ± 8051.64	877,199.02	100.00
		Scheme amount			4570.07± 8095.67	850,033.57	96.92
		Patient levy			146.05 ± 772.76	27,165.45	3.08
	4	Total cost	33	12.69	4716.12 ± 8051.64	40,360.69	100.00
		Scheme amount			1157.23 ± 2098.57	38,188.48	94.62
		Patient levy			±	2,172.21	5.38
Phase 3	1	Total cost	15	10.71	283.80 ± 246.60	4,257.07	100.00
		Scheme amount			170.03 ± 199.24	2,550.39	59.91
		Patient levy			113.78 ± 131.52	1,706.68	40.09
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	112	80.00	364.11 ± 350.15	40,780.71	100.00
		Scheme amount			355.89 ± 351.65	39,859.21	97.74
		Patient levy			8.23 ± 20.27	921.50	2.26
	4	Total cost	13	9.29	471.66 ± 464.38	6,131.63	100.00
		Scheme amount			374.37 ± 368.20	4,866.83	79.37
		Patient levy			97.29 ± 96.18	1,264.80	20.63

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of all Rx claimed during each phase.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.23.2 Average cost per prescription for Crohn's disease patients during phase 2 according to age

Phase	Medicines	Age group	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	*Biologics*	1	Total cost	25	20.00	8851.02 ± 1548.85	221,275.39	100.00
			Scheme amount			8851.02 ± 1548.85	221,275.39	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	95	76.00	9024.46 ± 9444.17	857,323.43	100.00
			Scheme amount			8773.22 ± 9615.63	833,456.37	97.22
			Patient levy			251.23 ± 1069.44	23,867.06	2.78
		4	Total cost	5	4.00	5993.84 ± 0.00	26,969.20	100.00
			Scheme amount			5993.84 ± 0.00	29,969.20	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
	Other	1	Total cost	16	11.85	504.95 ± 22.25	8,079.24	100.00
			Scheme amount			504.95 ± 22.25	8,079.24	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	91	67.41	218.41 ± 236.30	19,875.59	100.00
			Scheme amount			182.17 ± 188.74	16,577.20	83.48
			Patient levy			36.25 ± 95.34	3,298.39	16.52
		4	Total cost	28	20.74	371.12 ± 425.00	10,391.49	100.00
			Scheme amount			293.55 ± 337.63	8,219.28	79.10
			Patient levy			77.58 ± 87.69	2,172.21	20.90

Age group 1 = <25 years; Age group 2 = 25 – 39 years; Age group 3 = 40 – 64 years; Age group 4 = ≥ 65 years.

Frequency = number of prescriptions claimed per year.

SD = Standard Deviation.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.4.1 Average cost per prescription for Crohn's disease patients according to prescriber

Phase	Prescriber	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 1	**1**	Total cost	114	37.38	302.46 ± 244.12	34,480.22	100.00
		Scheme amount			285.36 ± 226.77	32,531.15	94.35
		Patient levy			17.10 ± 29.33	1,949.07	5.65
	2	Total cost	0	0	-	0.00	100.00
		Scheme amount			-	0.00	98.90
		Patient levy			-	0.00	1.10
	3	Total cost	88	28.85	400.76 ± 283.38	35,267.02	100.00
		Scheme amount			396.37 ± 286.98	34,880.20	94.81
		Patient levy			4.40 ± 22.65	386.82	5.19
	4	Total cost	103	33.77	376.14 ± 259.60	38,742.28	0.00
		Scheme amount			356.63 ± 241.00	36,732.82	0.00
		Patient levy			19.51 ± 39.77	2,009.46	0.00
	5	Total cost	0	0	-	0.00	100.00
		Scheme amount			-	0.00	98.87
		Patient levy			-	0.00	1.13
Phase 2	**1**	Total cost	44	16.92	3255.17 ± 14750.21	143,227.48	100.00
		Scheme amount			3218.24 ± 14756.66	141,602.38	99.97
		Patient levy			36.93 ± 85.27	1,625.10	0.03
	2	Total cost	0	0	-	0.00	100.00
		Scheme amount			-	0.0	96.32
		Patient levy			-	0.00	3.68
	3	Total cost	59	22.69	4281.72 ± 3995.27	252,621.60	0.00
		Scheme amount			4280.47 ± 3996.52	252,547.90	0.00
		Patient levy			1.25 ± 7.07	73.70	0.00
	4	Total cost	157	60.38	4783.86 ± 4324.01	751,065.26	100.00
		Scheme amount			4607.81 ± 4425.10	723,426.40	98.05
		Patient levy			176.04 ± 838.10	27,638.86	1.95
	5	Total cost	0	0	-	0.00	100.00
		Scheme amount			-	0.00	89.552
		Patient levy			-	0.00	10.48
Phase 3	**1**	Total cost	66	47.14	452.90 ± 398.55	29,891.70	100.00
		Scheme amount			444.09 ± 402.45	29,310.13	82.81
		Patient levy			8.81 ± 19.00	581.57	17.19
	2	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00
	3	Total cost	33	23.57	156.69 ± 180.37	5,170.69	100.00
		Scheme amount			140.26 ± 174.31	4,628.70	89.552
		Patient levy			16.42 ± 27.60	541.99	10.48
	4	Total cost	41	29.29	392.85 ± 314.45	16,107.02	100.00
		Scheme amount			325.31 ± 266.70	13,337.60	82.81
		Patient levy			67.55 ± 108.94	2,769.42	17.19

	5	Total cost	0	0	-	0.00	0.00
		Scheme amount			-	0.00	0.00
		Patient levy			-	0.00	0.00

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

% Rx = % of all Rx claimed during each phase.

% = percentage contribution of the medical aid scheme and patient to final cost.

Table A.34.4.2 Average cost per prescription for Crohn's disease patients during phase 2 according to prescriber

Phase	Medicines	Prescriber	Variables	Frequency (n)	% Rx	Mean ± SD	Total cost	%
Phase 2	***Biologics***	**1**	Total cost	2	1.60	66460.18 ± 31329.61	132,920.36	100.00
			Scheme amount			66460.18 ± 31329.61	132,920.36	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	30	24.00	8116.68 ± 965.59	243,500.43	100.00
			Scheme amount			8116.68 ± 965.59	243,500.43	100.00
			Patient levy			0.00 ± 0.00	0.00	0.00
		4	Total cost	93	74.40	7872.55 ± 2824.39	732,147.23	100.00
			Scheme amount			7615.92 ± 3273.71	708,280.17	96.74
			Patient levy			256.64 ± 1080.35	23,867.06	3.26
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
	Other	**1**	Total cost	42	31.11	245.41 ± 300.21	10,307.12	100.00
			Scheme amount			206.71 ± 226.32	8,682.02	84.23
			Patient levy			38.69 ± 86.92	1,625.10	15.77
		2	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00
		3	Total cost	29	21.48	314.52 ± 201.54	9,121.17	100.00
			Scheme amount			311.98 ± 201.36	9,047.47	99.19
			Patient levy			2.54 ± 10.00	73.70	0.81
		4	Total cost	64	47.41	295.59 ± 317.84	18,918.03	100.00
			Scheme amount			236.66 ± 263.26	15,146.23	80.06
			Patient levy			58.93 ± 106.60	3,771.80	19.94
		5	Total cost	0	0	-	0.00	0.00
			Scheme amount			-	0.00	0.00
			Patient levy			-	0.00	0.00

Prescriber type: 1 = General medicine practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

% Rx = % of total number of biologics and "other" prescriptions respectively.

% = percentage contribution of medical aid scheme and patient to final cost.

Table A.35 Average number of medicine items per prescription for Crohn's disease patients according to prescriber

Phase		Prescriber	Number of prescriptions	Number of medicine items	Average items per Rx Mean ± SD
Phase 1		**1**	114.00	225.00	1.97 ± 1.33
		2	0	0.00	-
		3	88.00	147.00	1.67 ± 0.83
		4	103.00	203.00	1.97 ± 1.18
		5	0	0.00	-
Phase 2	***Biologics***	**1**	2.00	3.00	1.50 ± 0.71
		2	0	0.00	-
		3	30.00	30.00	1.00 ± 0.00
		4	93.00	95.00	1.02 ± 0.15
		5	0	0.00	-
	Other	**1**	42.00	93.00	2.21 ± 1.52
		2	0	0.00	-
		3	29.00	35.00	1.21 ± 0.49
		4	64.00	128.00	2.00 ± 1.53
		5	0	0.00	-
Phase 3		**1**	66.00	144.00	2.18 ± 1.19
		2	0	0.00	-
		3	33.00	54.00	1.64 ± 0.90
		4	41.00	103.00	2.51 ± 1.90
		5	0	0.00	-

Prescriber type: 1 = General Medicine Practice; 2 = Neurology; 3 = Other; 4 = Phy/Im/Rheu/Neph/Diab/En; 5 = Radioth/Nuclmed/Oncology.

SD = Standard Deviation.

Table A.36.1 Average number of prescriptions per Crohn's disease patient

Phase	Frequency (Patients)	Sum (Rx)	Average Rx per patient Mean ± SD
Phase 2	11	125.00	11.36 ± 11.22

Table A.36.2 Average number of prescriptions per Crohn's disease patient according to gender

Phase	Gender	Frequency (Patients)	Average Rx per patient Mean ± SD	Sum (Rx)
Phase 2	**F**	6	15.17 ± 12.29	91.00
	M	5	6.80 ± 8.84	34.00

Table 36.3 Average number of prescriptions per Crohn's disease patient according to age

Phase	Age group	Frequency (Patients)	Average Rx per patient Mean ± SD	Sum (Rx)
Phase 2	**1**	3	8.33 ± 6.35	25.00
	2	0	-	0.00
	3	7	13.57 ± 13.39	95.00
	4	1	5.00 ± 0.00	5.00

APPENDIX C

Abstract submitted to and accepted by

ISPOR 13th Annual European Congress

MEDICINE TREATMENT COST OF RHEUMATOID ARTHRITIS BEFORE AND AFTER TREATMENT WITH BIOLOGICAL DRUGS

Roux, I., Lubbe, MS, Burger, JR, Lamprecht, JC,

[1]Medicine usage in South Africa, School of Pharmacy, North-West University, South Africa

OBJECTIVES: To investigate the medicine treatment cost of rheumatoid arthritis (RA) before and after treatment with biological drugs in the private health care sector of South Africa.

METHOD: A quantitative retrospective drug utilization review was performed on medicine claims data of a pharmacy benefit management company (PBM) in South Africa. Data for a four-year period (1 Jan 2005 to 31 Dec 2008) were used to determine the medicine treatment cost of 141 RA patients before and after treatment with biological drugs. The following biological drugs were prescribed to RA patients during the study period: Infliximab, adalimumab and etanercept.

RESULTS: Biological drugs prescribed to RA patients represented 0.28% (n = R20 708 818.82) of the total cost (N = R7 483 759 176.23) of all medication claimed through the PBM during the four year period. It further represented 81.43% of the total medicine treatment cost of RA patients (N = R25 432 294.04). The other medication (excluding biological drugs) prescribed to RA patients *before* starting with biological items represented 8.86% (n = R2 254 330.44) of the total medicine treatment cost of RA patients and those prescribed *after* treatment with biological represented 3.91% (n = R992 533.62). Both the number of prescriptions for other medication prescribed to RA patients and the average number of medicine items per prescriptions for these medications decreased from the period *before* to the period *after* treatment with biological drugs. The average number of medicine items per prescription decreased from 2.79 ± 2.3 *before* to 2.35 ± 1.86 *after* treatment with biological drugs. The average cost per biological drug (i.e., R8 073.61 ± 2210.46) was practically significant higher compared to the average cost of the other medication prescribed *before* (R128.45 ± 155.93) and *after* (R198.66 ± 888.31) treatment with biological drugs.

CONCLUSION. Although biological drugs used in the treatment of RA are very expensive, it seems that number of other medication prescribed to RA patients decreased after treatment with biological drugs, which may influence the medicine treatment cost of these patients.

From: <stuckerson@ispor.org>

To: <20098871@nwu.ac.za>

Date: 7/30/2010 3:23 PM

Subject: ISPOR 13th Annual European Congress Poster Presentation Acceptance

Dear Ilanca Roux:

Congratulations. The abstract titled: MEDICINE TREATMENT COST OF RHEUMATOID ARTHRITIS BEFORE AND AFTER TREATMENT WITH BIOLOGICAL DRUGS for which you are listed as a contributing author was accepted as a POSTER PRESENTATION during the following session:

POSTER SESSION I

Sunday, 7 November 2010

12:00 - 20:00

for presentation at the ISPOR 13th Annual European Congress to be held 6-9 November 2010 at the Prague Congress Centre in Prague, Czech Republic.

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Thank you again for your contribution to health care in the scientific community.

Sincerely,

Jan J.V. Busschbach PhD, Research Review Committee Co-Chair & Interim Director, Department of Medical Psychology & Psychotherapy, Erasmus MC, Rotterdam, The Netherlands

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