OVERVIEW OF THE PRESCRIBING PATTERNS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: 2004-2006

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ABSTRACT

Title: Overview of the prescribing patterns of non-steroidal anti-inflammatory drugs: 2004-2006.

Key words: Non-steroidal anti-inflammatory drugs (NSAIDs), Coxibs, gastro-intestinal, drug utilisation, cost, pharmacoeconomics.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for systemic control of acute and chronic pain and inflammation (Lin *et al.*, 2000:1129), but usage problems and side-effects that occur during the post-marketing phase of these drugs are well documented (Thiefin & Beaugerie, 2005:287). Following the demonstration of the value of anti-inflammatory therapy in diseases like rheumatoid arthritis (Boardman & Dudley Hart, 1967:268), new NSAIDs appeared on the market (Dieppe *et al.*, 2004:867), and the indications steadily broadened from inflammatory diseases to almost any painful condition. Studies have indicated that NSAID-associated serious upper gastro-intestinal (GI) adverse events result in 103 000 hospitalisations (Bombardier, 2002:4) and 165 000 deaths per year in the United States.

A study in South Africa in 2002 indicated that NSAID utilisation contributed considerably to the total cost of all medicine items from a medicine claim database in the private health care sector (Joubert, 2002:260).

The objective of this study was to determine the prevalence and cost of non-steroid anti-inflammatory drugs in a section of the private health care sector, and specifically to determine the prevalence, usage and cost of Coxib (Specific cyclo-oxygenase-2 inhibitor) medicine items before and after the withdrawal of Vioxx® from the market in September 2004 (Merck, 2004).

Data from two medicine claim databases for the years 2004, 2005 and 2006 (medicine claim database I) and the years 2005 and 2006 (medicine claim database M), were analysed by means of a retrospective drug utilisation review (DUR) study. The usage of Coxib medicine items was determined, and compared for the periods before and after the withdrawal of Vioxx® in September 2004.

It was found that between 9 and 10.5 per cent of prescriptions dispensed through both medicine claim database I and medicine claim database M during the study period were NSAID prescriptions. NSAID medicine items on medicine claim database I represented between 3.9 % (R25 942 986) and 2.9 % (R8 073 034) of the total cost of all medicine items claimed from 2004 to 2006. NSAIDs represented 3.1 % (R58 290 412) and 2.8 % (R57 752 267) of the cost of all medicine items claimed through medicine claim database M during 2005 and 2006 respectively, indicating similar trends in the two medicine claim databases.

The prevalence of Coxibs on medicine claim database I decreased from almost 20 % (47 938) in 2004 to 8.4 % (13 276) in 2005, but showed an increase again to 10.9 % (12 355) in 2006. The prevalence of both cyclo-oxygenase (COX) inhibitors, and Coxibs demonstrated a change during 1 September 2004 to 31 December 2004 when COX-inhibitors showed an increase in use, while Coxibs showed and almost equal but opposite trend with a decrease in use. This could possibly be related to perceptions of providers and public with regard to Coxibs and their related safety after the withdrawal of Vioxx® on 30 September 2004 (Merck, 2004) and other Coxibs such as Bextra® (FDA, 2005) in 2005 in USA.

It is concluded that most patients who were using Coxibs before the withdrawal of Vioxx®, substituted Coxibs for COX-inhibitors, that are known for their possible gastro-intestinal side-effects.

Recommendations for future research regarding NSAID use were also made, and included an investigation of the usage of Coxibs in different age groups, as well as the combination of NSAIDs with gastro-protective medicines in long-term use.

OPSOMMING

Titel: 'n Oorsig oor die voorskryfpatrone van nie-steroïed anti-inflammatoriese middels: 2004-2006

Sleutelwoorde: Nie-steroïed anti-inflammatories middels (NSAIMs), koksibbe, gastro-intestinaal, medisyneverbruik, koste, farmako-ekonomie.

Nie-steroïed anti-inflammatoriese middels (NSAIMs) word algemeen vir die sistemiese behandeling van akute en kroniese pyn en inflammasie gebruik (Lin *et al.*, 2000:1129), maar probleme en newe-effekte wat in die fase na bemarking van hierdie middels voorgekom het, is goed gedokumenteer (Thiefin & Beaugerie, 2005:287). Nadat die waarde van anti-inflammatoriese behandeling vir siektes soos rumatoïede artritis aangetoon is (Boardman & Dudley Hart, 1967:268), het daar nuwe NSAIMs op die mark verskyn (Dieppe *et al.*, 2004:867) en die indikasies het vanaf inflammatoriese siektes tot bykans enige pynlike toestand uitgebrei. Studies toon dat effekte van NSAIMs op die boonste gastro-intestinale (GI) weg die oorsaak van ongeveer 103 000 hospitalisasies en 165 000 sterftes per jaar in die Verenigde State is (Bombardier, 2002:4).

'n Studie in 2002 in Suid-Afrika het getoon dat gebruik van NSAIMs grootliks tot die totale koste van alle medisyne-items in 'n databasis van medisyne-eise in die private gesondheidsorgsektor bygedra het (Joubert, 2002:260).

Die doel van hierdie studie was om die voorkoms en koste van nie-steroïed anti-inflammatoriese middels in 'n deel van die private gesondheidsorgsektor te bepaal, en spesifiek die voorkoms, gebruik en koste van koksibbe (spesifieke siklo-oksigenase-2 remmers) voor en na die ontrekking van Vioxx® vanaf die mark in September 2004 (Merck, 2004).

Data vanaf twee databasisse van medisyne-eise vir die jare 2004, 2005 en 2006 (databasis I van medisyne-eise) en die jare 2005 en 2006 (databasis M van medisyne-eise) is met behulp van 'n retrospektiewe evaluering van geneesmiddelgebruik ontleed. Die verbruik van koksibbe is bepaal en vir die periodes voor en na die onttrekking van Vioxx® in September 2004 (Merck, 2004) vergelyk.

Dit is gevind dat tussen 9 en 10.5 persent van alle voorskrifte wat tydens die studieperiode in sowel databasis I as M opgeneem is, voorskrifte vir NSAIM's was. NSAIMs in databasis I verteenwoordig tussen 3.9 % (R25 942 986) en 2.9 % (R8 073 034) van die totale koste van alle medisyne-items wat gedurende 2004 tot 2006 geëis is. NSAIMs het 3.1 % (R58 290 412) en 2.8 % (R57 752 267) van die koste van alle medisyne-items in databasis M gedurende 2005 en 2006 onderskeidelik verteenwoordig, wat aandui dat die twee databasisse soortgelyke verbruikspatrone vertoon.

Die voorkoms van koksibbe in databasis I het vanaf ongeveer 20 % (47 938) in 2004 na 8.4 % (13 276) in 2005 afgeneem, maar toon 'n toename na 10.9 % (12 355) in 2006. Die voorkoms van sowel siklo-oksigenase (COX) remmers as koksibbe vertoon 'n verandering in verbruik in die periode van 1 September 2004 tot 31 Desember 2004. In hierdie periode het COX-remmers 'n toename in verbruik getoon, terwyl koksibbe 'n gelyke, maar teenoorgestelde afname in verbruik getoon het. Hierdie verandering kan verband hou met die persepsie van verskaffers en die publiek oor die veiligheid van koksibbe na die onttrekking van Vioxx® op 30 September 2004 (Merck, 2004) en ander koksibbe soos Bextra® (FDA, 2005) in 2005 in die VSA.

Die gevolgtrekking is gemaak dat pasiënte wat koksibbe voor die onttrekking van Vioxx® gebruik het, hierdie koksibbe vervang het met COX-remmers wat bekend is vir hul moontlike gastro-intestinale newe-effekte.

Aanbevelings vir toekomstige navorsing oor NSAIM's is ook gemaak, en sluit in 'n ondersoek na die gebruik van koksibbe in verskillende ouderdomsgroepe, sowel as die kombinasie van NSAIM's met gastro-beskermende medisyne vir langtermyngebruik.

The life of every man is a diary
In which he means to write one story
And writes another
And his humblest hour
Is when he compares the volume
As it is with what he hoped to make it

ψ James M Berrie ψ

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION AND PROBLEM STATEMENT

Although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for systemic control of acute or chronic pain and inflammation (Lin *et al.*, 2000:1129), usage problems and serious side-effects still occur during the post-marketing phase of these drugs (Thiefin & Beaugerie, 2005:287). This study investigated the general usage patterns of NSAIDs over a two-year time period in a section of the private health care sector.

Following the demonstration of the value of anti-inflammatory therapy in disease like rheumatoid arthritis (Boardman & Dudley Hart, 1967:268), most pharmaceutical companies began to develop NSAIDs of their own (Jüni & Dieppe, 2004:100).

According to Dieppe *et al.* (2004:867) as new NSAIDs appeared, the indications steadily broadened from inflammatory diseases to almost any painful condition. Each time a new drug was launched the market expanded, resulting in annual estimated sales of more than $20 billion (bn) worldwide.

Joubert (2002:260) found that NSAID utilisation in South Africa, contributes considerably to the total cost of all the medicine items from a medicine claim database (period 1 July 1999 to 30 June 2000), where NSAIDs prescriptions constitute a total prevalence of 10.04 % (n=1 525 981) of all the prescriptions, and where NSAID items have a total prevalence of 4.99 % (n=3 261 639) with a cost of 4.38 % (n=R416 919 997.00) for all the medicine items. It was further found that the majority of NSAIDs prescribed during the twelve-month period were for innovator products, with a prevalence of 54.96 % (n=162 807) and a cost of 61.71 % (n=R18 259 101.90). Joubert (2002:260) found that quite a number of prescriptions containing innovator NSAIDs could be generically substituted, and R273 709.52 in cost expenditure could have been saved over a twelve-month period of the study.

Spiegel *et al.* (2006:27) state that NSAIDs are the most commonly used medications for chronic arthritis, accounting for 111 million prescriptions annually and 3 % of the American prescription drug market. The analysis of Spiegel *et al.* (2006:27) reveals that the NSAID plus proton-pump inhibitors (PPI) strategy may be superior to selective Specific Cyclo-oxygenase-2 inhibitors (Coxibs) in minimising incident dyspeptic symptoms during the treatment of chronic arthritis. Given the high prevalence and expense of dyspeptic symptoms, their data further the argument that NSAID plus PPI therapy may be preferred over Coxibs in the treatment of patients with arthritis at high risk for adverse gastro-intestinal events.

Sturkenboom *et al.* (2002:132) state that medical interventions for upper gastro-intestinal disorders following NSAID treatment include prescriptions for gastro-protective drugs (such as antacids, misoprostol and proton-pump inhibitors), hospitalisations, and outpatient diagnostic procedures. The cost of medical interventions for gastro-intestinal events added 58 % to the cost of NSAID therapy. Sturkenboom *et al.* (2002:132) found that 12.4 % of the patients accounted for the iatrogenic costs, where 77 % of the patients had a positive history of gastro-intestinal disorders and 82 % were older than 50 years of age. Co-prescriptions for gastro-protective drugs accounted for 78.6 % of the overall iatrogenic costs.

In Italy, the iatrogenic costs of NSAID therapy add 58 % to the cost of NSAID treatment; most of the cost is generated by co-prescriptions of gastro-protective drugs to elderly NSAID users or patients with a history of gastro-intestinal disorders (Sturkenboom *et al.*, 2002:132).

On September 30, 2004 Merck® Pty announced the voluntary worldwide withdrawal of VIOXX® (rofecoxib) from the market. According to Merck® Pty, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX® compared to those taking placebo (Merck, 2004).

The removal of rofecoxib (Vioxx®) from the market and the debate around Coxibs for the last few years should encourage rheumatologists to reappraise the risk/benefit ratio of each NSAID prescription. The variable severity of disorders treated with NSAIDs complicates this task. Therefore, prescriptions should be written on a case-by-case basis, taking into account the expected symptomatic effect of the medication, the disorder being treated, its impact on quality of life, and the availability of other treatment options. At the same time, consideration should be given to each of the known side-effects (e.g., gastro-intestinal toxicity and cardiovascular events) and to their expected frequency given patient-related risk factors and treatment duration (Berenbaum, 2005:2)

Against this background, it is imperative that research be conducted regarding the utilisation and cost implications associated with NSAIDs, in the private health care sector of South Africa.

1.2 RESEARCH QUESTIONS

The following research questions can be formulated against this background for the proposed study periods 2004 to 2006 for Medicine claim database I, and 2005 to 2006 for Medicine claim database M:

- What is the prevalence of the usage of selective Coxibs before and after the discontinuing of Vioxx®?
- What is the prevalence of the usage of non-steroidal anti-inflammatory drugs and what are the costs associated with these drugs?

1.3 RESEARCH OBJECTIVES

1.3.1 General objective

The general objective of this study was to review certain prescribing and cost patterns of non-steroidal anti-inflammatory drugs in a section of the private health care sector for the period 2004 to 2006 by using two different medicine claim databases.

1.3.2 Specific objectives

The research objectives consisted of two phases, namely a literature review, and an empirical investigation. The specific research objectives of the two phases included the following:

The specific objectives of the literature study included the following:

- To conceptualise the usage and side-effects of NSAID use
- To review specific cyclo-oxygenase-2 inhibitor (Coxib) use and the aspects associated with the withdrawal of these products from the market.
- To conceptualise from the literature what managed health care, drug utilisation, pharmacoeconomics and disease management entail.

The specific objectives of the empirical study for both databases included the following:

- To investigate the usage patterns of NSAID therapy over the study period.
- To analyse and calculate the cost of NSAID therapy over the study period.
- To review the use of Coxibs before and after the discontinuing of Vioxx® (refer to paragraphs 2.1.6.3 and 2.1.6.4) on Medicine claim database I.
- To investigate the usage patterns of Coxib therapy.
- To analyse and calculate the cost of Coxib therapy.

- To investigate the usage patterns of NSAID therapy per sub-pharmacological group (according to MIMS classification) over the study period.
- To analyse and calculate the cost of NSAID therapy per sub-pharmacological group (according to MIMS classification) over the study period.
- To identify the top twenty NSAIDs according to prevalence, cost and gender for Medicine claim database M.
- To identify and analyse the number of NSAID containing prescriptions per patient for Medicine claim database M.
- To identify the prevalence of NSAID use according to active ingredient for medicine claim database M.
- To investigate the prevalence and cost of NSAID medicine items according to age for medicine claim database M.

1.4 RESEARCH METHOD

1.4.1 Literature review

The literature review consisted of pharmacoeconomics, pharmacoepidemiology and drug utilisation review for optimum health care as well as the gastric- and toxic effects of NSAIDs and the treatment thereof. The use of Coxibs as well as their withdrawal from the market was investigated and discussed.

1.4.2 Empirical investigation

The research was compiled from both Medicine claim database I and Medicine claim database M, during the periods of 1 January 2005 to 31 December 2006 for Medicine claim database M, and 1 January 2004 to 31 December 2005 for Medicine claim database I. The total study was comprised of all patients that had used one or more NSAID during the specific study period. This was a retrospective DUR study. A discussion of the empirical investigation can be found in chapter 3 under the following headings:

- Introduction
- Aims and objectives
- Research design

- Research methodology
- Data analysis
- Measuring criteria for data analysis
- Reliability and validity

The personal information of patients and prescribers were not disclosed due to ethical reasons. The two pharmacy benefit management companies (PBMs) gave permission for the data to be used in this study, and the ethical committee of the North-West University approved the study (NWU-0046-08-S5).

1.5 DIVISION OF CHAPTERS

Chapter 1 – Introduction

Chapter 2 – An overview of the prevalence, use, clinical effects and pharmacoeconomic aspects of non-steroidal anti-inflammatory drugs (NSAIDs)

Chapter 3 – Empirical investigation

Chapter 4 – Results and discussion

Chapter 5 – Conclusions and recommendations

1.6 CHAPTER SUMMARY

In this chapter, the problem statement, research questions and objectives, research methods, and the division of chapters have been outlined.

CHAPTER 2: AN OVERVIEW OF THE PREVALENCE, USE, CLINICAL EFFECTS AND PHARMACOECONOMIC ASPECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

2.1 THE PREVALENCE, USE AND CLINICAL EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

2.1.1 INTRODUCTION

Salicylates and other related agents used in the treatment of rheumatic disease share the ability to suppress the signs and symptoms of inflammation. These drugs also exert antipyretic and analgesic effects, but it is their anti-inflammatory properties that make them most useful in the management of disorders in which pain is related to the intensity of the inflammatory process (Wagner *et al.*, 2004:577).

The treatment of patients with inflammation involves two major goals i.e. the relief of pain, which is often the presenting symptom and the main continuing complaint of the patient as well as the slowing or arrest of the tissue-damaging process (Wagner *et al.*, 2004:577).

2.1.2 CHRONIC USE OF NSAIDs

NSAIDs are used for a variety of diseases, but the most common among these are osteoarthritis and rheumatoid arthritis.

2.1.2.1 Osteoarthritis

2.1.2.1.1 Definition

Osteoarthritis (OA) is a common, slowly progressing disorder affecting primarily the weight-bearing joints. It is characterised by degeneration of the articular cartilage and sub-chondral bone resulting in osteophyte formation, pain, stiffness, and progressive disability. Inflammatory mediators may increase inflammatory and degenerative responses (Rizzo, 2005:1429).

According to Haq *et al.* (2003:377), 10 % to 15 % of adults older that 60 years have some form of osteoarthritis, a disease that is becoming ever more important in an ageing population. It

ranks second only to cardiovascular disease in producing severe chronic disability in the elderly (Hansen & Elliott, 2005:1685).

2.1.2.1.2 Epidemiology

Osteoarthritis (OA) remains the most prevalent of the rheumatic diseases and a common cause of disability and decreased worker productivity. The disease prevalence (Hansen & Elliott, 2005:1685) increases with age, affecting individuals in the middle to later years of life. Radiographic data confirm the presence of OA at some site in the body in the majority of individuals older than 65 years of age and in more than 80 % of those aged 75 and older.

2.1.2.1.3 Prevalence by age, gender and race

According to Rizzo (2005:1429), men are affected at a younger age more commonly than women, but the rate of women affected exceeds that of men by middle age. The Centre for Disease Control (CDC, 2007) states that women have higher rates of osteoarthritis than men, especially after 50 years of age. Rizzo (2005:1429) also states that OA of the hand is almost twice as common in women than men, and is more common among white women, whereas osteoarthritis of the knee is more common in black women.

The CDC (2007) states that approximately 13.9 % of Americans aged 25 years and older, and approximately 33.6 % (12.4 million) aged 65 years and older are affected by osteoarthritis. The overall number of adults affected by osteoarthritis has gone up from 21 million in 1990 to an estimated 26.9 million in 2005. In the younger than 45-year-old group, 19.3 % of hands and 23.9 % of feet were categorised as mild to severe. By comparison, in the 75- to 79-year-old group, 85 % (Hansen & Elliott, 2005:1686) showed the same percentage of change in the hands (refer to p. 9 – signs/physical examination). OA of the knee also increased from less than 0.1 % in people between the ages of 23-34 to 10-20 % for those 65-74 years old. Likewise the proportion of individuals with OA classified as moderate to severe increased with age, reaching 33 % for knees and about 50 % for hips for individuals between 65 and 74 years of age (Hansen & Elliott, 2005:1686).

2.1.2.1.4 Risk Factors

According to Haq *et al.* (2003:378), major risk factors for OA include the following:

- Obesity
- Occupation, sports and trauma
- Genetic factors
- Osteoporosis and bone density
- Trauma
- Age

(Haq *et al.*, 2003:378)

2.1.2.1.5 Pathophysiology

The etiology of osteoarthritis covers a wide range and consists of mechanical, biochemical and genetic factors. According to Martel-Pelletier (2004:s31), the disease progression can be divided into the following three stages:

Stage 1 – the proteolytic breakdown of the cartilage matrix

Stage 2 – the fibrillation and erosion of cartilage surface, and the release of breakdown products into the synovial fluid.

Stage 3 – the synovial inflammation sets in at this stage due to the ingestion of breakdown products by the synovial cells through phagosytosis to produce proteases and pro-inflammatory cytokines.

2.1.2.1.6 Clinical Presentation

The clinical presentation depends on the duration of disease, the joints affected and the severity of joint involvement. The predominant symptom is a localised deep, aching pain associated with the affected joint (Hansen & Elliott, 2005:1689).

Clinical presentation of osteoarthritis

According to Hansen and Elliott (2005:1689) and Manek and Lane (2000:1796) the clinical presentation of osteoarthritis consists of the following features:

- **Age:** Harms *et al.* (2007:23) concur with Hansen and Elliott (2005:1689) that osteo-arthritis (OA) is commonly found among elderly patients.

- **Gender:** Under the age of 45 years osteoarthritis is more common in men, but over the age of 45 years it is more commonly found in women (Hansen & Elliott, 2005:1689).
- **Symptoms:** The most frequent complaint is pain. This includes, but is not limited to, deep aching and pain on motion. Early in the course of the disease, pain occurs when the joint is first used and is relieved by rest or removal of weight from the affected joint. Later, the pain occurs with minimal motion or activity and may be present during rest. Stiffness can occur, but is localised to the involved joints and rarely exceeds 15minutes in duration. Weather or changes in the barometric pressure also seem to aggravate the pain associated with OA (Hansen & Elliott, 2005:1689). Other symptoms include limited joint motion, an instability of the weight-bearing joints, crepitus and crackling (Manek & Lane, 2000:1796).
- **Signs/Physical examination:** - Upon physical examination monoarticular or oligoarticular, asymmetrical involvement of the joints can be found (Hansen & Elliott, 2005:1689). Joints frequently involved include the following:
    - The hands – the distal interphalangeal (DIP) and proximal interphalangeal (PIP) first carpometacarpal joints
    - The foot – the first metatarsophalangeal joint
    - The hips, knees, cervical spine, lumbar spine
    - Observations on joint examination show bony proliferation or occasional synovitis, local tenderness, crepitus, muscle atrophy, limited motion with passive/active movement and effusions
- **Laboratory values:** There is no specific test for diagnosing osteoarthritis (Hansen & Elliott, 2005:1689).

2.1.2.1.7 Desired outcome

The major goals for the management of osteoarthritis are to educate the patient, caregivers, and relatives; relieve pain and stiffness; maintain or improve joint mobility; limit functional impairment; and maintain or improve quality of life (Wells *et al.*, 2003:10). Treatment according to Hansen and Elliott (2005:1690), should be tailored to each individual.

2.1.2.1.8 Pharmacologic therapy

Drug therapy in OA is targeted at relief of pain. Because OA often occurs in older individuals who have other medical conditions, a conservative and individualised approach to treatment is necessary, and appropriate non-drug therapies should be continued after drug therapy has been initiated (Wells *et al.*, 2003:10). According to the American College of Rheumatology (ACR) acetaminophen should be used as initial systemic treatment of OA, as it may be as effective and less toxic than NSAIDs (Rizzo, 2005:1432).

2.1.2.1.9 Treatment

Wells *et al.* (2003:10) identify the major goals as educating the patient, care-givers and relatives; relieving symptoms such as pain and stiffness; preserving the joint motion and function by limiting disease progression; and minimising the disability.

According to Hansen and Elliott (2005:1689), the osteoarthritis treatment for each patient depends on the distribution and severity of joint involvement, other disease states, associated medications, and allergies. Osteoarthritis treatment should start with an understanding of the disease, physical therapy and regular exercise, rest, and weight loss if necessary. Figure 1, as adapted from Wells *et al.* (2003:12) and Boh (1997:1746), shows a detailed, step-by-step suggested treatment plan for osteoarthritis. Although Figure 1 shows acetaminophen or aspirin as the first drug choices for the treatment of OA, NSAIDs are the most commonly used and most effective drugs for the treatment of OA. NSAIDs are possibly placed second to acetaminophen due to its GI side-effects.

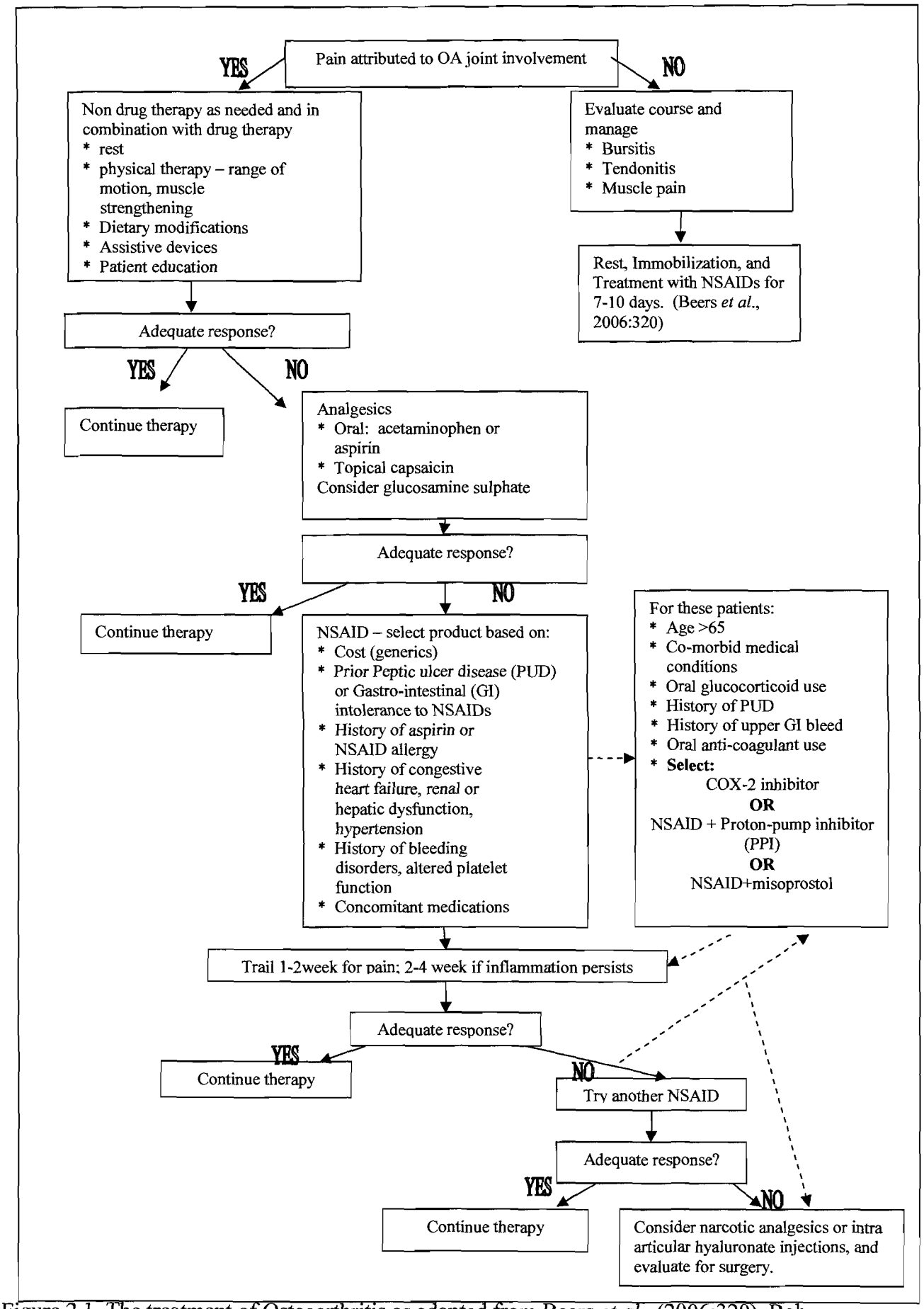

Figure 2.1 The treatment of Osteoarthritis as adapted from Beers *et al.*, (2006:320), Boh (1997:1746) and Wells *et al.* (2003:12).

2.1.2.2 Rheumatoid Arthritis

2.1.2.2.1 Definition

Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder of unknown aetiology characterised by polyarticular symmetric joint involvement and systemic manifestations (Wells *et al.*, 2003:28).

Extra-articular involvement including rheumatoid nodules, vasculitis, eye inflammation, neurologic dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly are manifestations of the disease. Although the usual disease course is chronic, some patients will spontaneously enter a remission (Schuna. 2005:1671).

2.1.2.2.2 Epidemiology

According to Rizzo (2005:1418), rheumatoid arthritis affects 0.3 % to 1.5 % of the population with women affected 2 to 3 times more frequently than men. In people aged 15-45 years of age, women predominate by a 6:1 ratio (Schuna, 2005:1671). The disease prevalence increases with age although it occurs in all age groups, and has a peak incidence in women between the ages of 40 and 60 years with the onset at 30 to 50 years (Rizzo, 2005:1418).

2.1.2.2.3 Pathophysiology

The immune system is a complex network of checks and balances designed to discriminate self from non-self (foreign) tissue. It helps to rid the body of infectious agents, tumour cells and products associated with the breakdown of cells. In rheumatoid arthritis this system no longer can differentiate self from non-self tissues and attacks the synovial tissue and other connective tissues (Schuna, 2005:1671).

According to Wells *et al.* (2003:28) most patients produce anti-bodies called rheumatoid factors; these sero-positive patients tend to have a more aggressive course than patients who are sero-negative. Wells *et al.* (2003:28) also state that chronic inflammation of the synovial tissue lining the joint capsule results in tissue production (pannus formation). Pannus invades cartilage and ultimately the bone surface, causing erosions of bone and cartilage and leading to joint destruction. The result may be loss of joint space and motion, bony fusion (ankylosis), joint subluxation, tendon contractures, and chronic deformity.

2.1.2.2.4 Clinical presentation

According to Schuna (2005:1673), the symptoms of rheumatoid arthritis normally develop over several weeks to months, and initial symptoms include fatigue, weakness, low-grade fever, loss of appetite, and joint pain. Schuna (2005:1673) also found that stiffness and muscle ache (myalgias) may precede the development of joint swelling (synovitis). Rizzo (2005:1419) concur with Schuna *et al.* (1997:1719) that the onset of rheumatoid arthritis is marked by systemic manifestations that include, but is not limited to, fatigue, depression, anxiety, anorexia, weight loss, aching and stiffness.

2.1.2.2.5 Joint involvement

According to Rizzo (2005:1419), the most commonly affected joints with rheumatoid arthritis are those of the fingers, hands, wrists, knees and feet. As the disease progresses other diarthrodial joints (elbows, shoulders etc.) joints may also become involved. Rizzo (2005:1419) also states that patients may complain of joint pain and stiffness that may last from 30 minutes to several hours. The limitation of joint motion that occurs early in the disease usually is because of pain, but later it is because of fibrosis.

Table 2.1 The functional classifications of rheumatoid arthritis (RA) taken from Schuna *et al.* (1997:1721)

Class I	Capable of all activities without handicap
Class II	Able to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
Class III	Functional capacity only adequate to perform a few of the normal duties of usual occupation
Class IV	Bed or confined to wheelchair, capable of little or no self-care

2.1.2.2.6 Desired outcome

The ultimate goal of RA treatment is to induce a full remission, although this is rarely achieved. The main objectives are to reduce joint swelling; stiffness; pain; preserve range of motion and

joint function; improve quality of life; prevent systemic complications; and slow destructive joint changes (Wells *et al.*, 2003:30).

2.1.2.2.7 Pharmacologic therapy

According to Rizzo (2005:1421), NSAIDs possess both analgesic and anti-inflammatory properties, and are accepted as first-line therapy for the symptomatic treatment of mild rheumatoid arthritis, however, Wells *et al.* (2003:30) state that they do not slow disease progression or prevent bony erosions or joint deformity. The primary objective of rheumatoid arthritis treatment is to improve and maintain functional status and therefore to improve the quality of life (Schuna, 2005:1675).

When used as primary therapy, NSAIDs should be given on a scheduled basis (Wells *et al.*, 2003:30) in anti-inflammatory doses and should not be used as monotherapy for more than three months unless the patient shows an adequate response. The majority of rheumatologists advocate early combination therapy with disease-modifying anti-rheumatic drugs (DMARDs) except where the disease is very minimal. Figure 2.2 shows a protocol for the treatment of rheumatoid arthritis adapted from Wells *et al.* (2003:31).

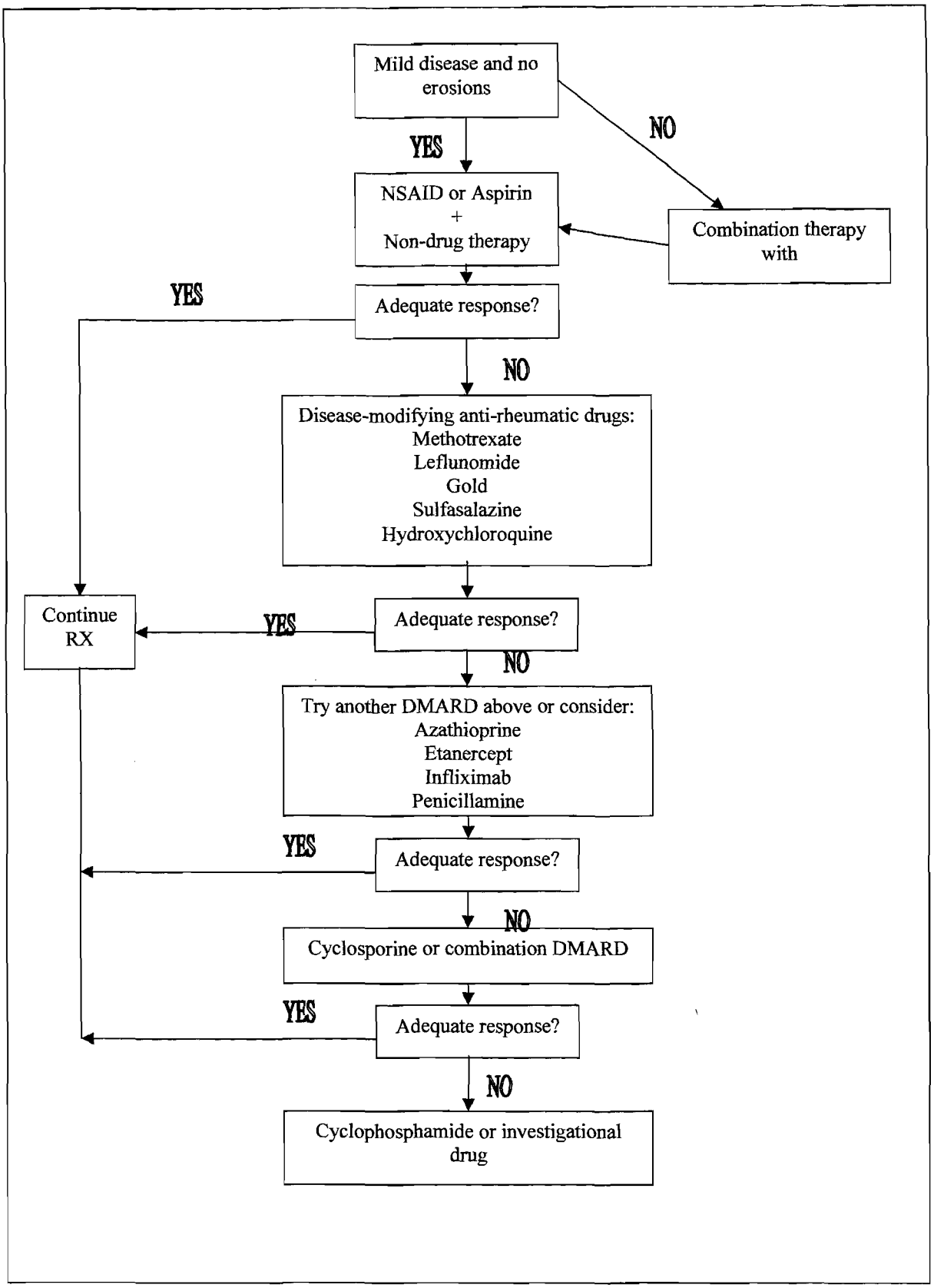

Figure 2.2 An algorithm for the treatment of rheumatoid arthritis (Wells *et al.*, 2003:31).

*DMARD= disease modifying anti-rheumatic drugs

One in five (over 21 %) of adults in the United States, according to the National Health Interview Survey (NHIS), reported having-doctor diagnosed arthritis during 2003-2005 (CDC, 2006:1089). The NHIS also found that 50 % of adults over 65 years of age, for the same time period, reported arthritis diagnosis. It is estimated that by 2030, approximately 67 million Americans 18 years and older, could be diagnosed with arthritis.

Table 2.2 Estimates of doctor-diagnosed arthritis and arthritis attributable activity (e.g. RA, gout, lupus, fibromyalgia etc.) – National Health Interview Survey, United States, 2003-2005 (CDC, 2006:1091)

Characteristic		**Doctor diagnosed arthritis (46.4 million persons)**
Gender:		
	Men	17.6 %
	Women	25.4 %
Age (years):		
	18-44	7.9 %
	45-64	29.3 %
	65+	50.0 %
Race/Ethnicity:		
	White, non-Hispanic	24.3 %
	Black, non-Hispanic	19.2 %
	Hispanic	11.4 %
	Other non-Hispanic	14.7 %
Body mass index (BMI*):		
	Underweight/Normal weight	16.3 %
	Overweight	21.7 %
	Obese	31.6 %
Physical activity level:		
	Inactive	25.0 %
	Active	19.5 %
Total:		21.6 %

*BMI = weight (kg) / height (m^2). Underweight/normal weight, ≤24.9; overweight, 25.0-29.9; and obese, ≥30.0.

In the USA the CDC (2007) estimated that 21 million adults have osteoarthritis and 2.1 million adults are affected by rheumatoid arthritis. The CDC also reported an estimated 5.1 million adults diagnosed with gout and an estimated 3.7 million adults with fibromyalgia.

Dominick *et al.* (2003:1568), compared men and women and found that women on average had a notably lower income, were more likely to have a history of GI events, and were more probable to report arthritis as an activity-restrictive health condition.

2.1.3 ACUTE USE OF NSAIDs

NSAIDs are well-known for their analgesic, antipyretic and especially anti-inflammatory abilities (Gibbon, 2008:369). More than two decades ago these properties enabled them to be used for a variety of conditions including, *inter alia*, arthritis (osteoarthritis, rheumatoid arthritis, psoriatic arthritis, juvenile chronic arthritis, and Reiter's syndrome), dental and bone pain (including pain of bone metastases), dysmenorrhoea, headaches, gout, Bartter's syndrome (Evans, 1984:52), trombo-embolic disorders, and relief of pain and inflammation. However, some of them could also be used for other purposes such as the closure of patent ductus arteriosus in premature infants (Gibbon, 2005:350). Evans (1984:52) reported that in the 1980s animal and human studies were also being done on the use of NSAIDs in cancer, diabetes, psoriasis, and shock, to name a few. According to Gasparini *et al.* (2004:531), NSAIDs might be beneficial in the prevention of Alzheimer's disease. However, much is still unknown, and ongoing clinical trials will be necessary (Gasparini *et al.*, 2004:531). In a population-based cohort study done by In't veld *et al.* (2001:1520), it was found that long-term use of NSAIDs may have a beneficial effect on the risk of Alzheimer's disease, but do not offer protection against vascular dementia.

According to Davies *et al.* (2000:137), an NSAID's clinical utility is evaluated through the balance between its therapeutic efficacy and toxicity. If an NSAID is effective but its side-effects cannot be tolerated by the patient, then it is of little use to the patient. Safety should be a primary consideration when an NSAID is chosen for a patient.

2.1.4 AN EXAMPLE OF CLASSIFICATION OF NSAIDs USED IN THE TREATMENT OF RHEUMATOID- AND OSTEO-ARTHRITIS

Table 2.3 The classification of non-steroidal anti-inflammatory drugs (NSAIDs) adapted from Gibbon (2005:352-358); Mayhew (2007:341) and Snyman (2007:97).

Class	Active ingredient	Example of Trade name	Dosage	Frequency
COX inhibitors	Diclofenac	Voltaren®	25-50mg	3 times daily
	Indometacin	Indocid®	25-50mg	3 times daily
	Ketorolac	Tora-dol®	10mg	3 times daily
	Ibuprofen	Brufen®	400-1000mg	3 times daily
	Naproxen	Naprosyn®	250-500mg	2 times daily
	Oxaprozin	Deflam®	1200mg	Daily
	Ketoprofen	Ketoflam®	100mg	2 times daily
	Sulindac	Adco-Sulindac®	100-200mg	2 times daily
	Nabumetone	Relafen®	500-1000mg	2 times daily
	Mefenamic acid	Ponstan®	500mg	3 times daily
	Lornoxicam	Xefo®	4-8mg	2 times daily
	Piroxicam	Feldene®	10-30mg	Daily
Selective COX-2 inhibitors	Meloxicam	Mobic®	7.5-15mg	Daily

Class	Active ingredient	Example of Trade name	Dosage	Frequency
Specific Cyclo-oxygenase-2 inhibitors (Coxibs)	Celecoxib	Celebrex®	100-200mg	2 times daily
	Lumiracoxib*	Prexige®	100-400mg	Daily
	Parecoxib	Rayzon®	20-40mg	2 times daily
	Valdecoxib*	Bextra®	40mg	Daily
	Rofecoxib*	Vioxx®	12.5-25mg	Daily

* These drugs have been withdrawn from the South African market (refer to paragraph 2.1.6.4).

2.1.5 SIDE-EFFECTS AND COMPLICATIONS OF NSAID THERAPY

2.1.5.1 Introduction

Historically these drugs were considered safe agents with little toxicity when they were first marketed in the 1970s (Evans, 1984:52). Currently upper gastro-intestinal (UGI) complications are well-recognised adverse events associated with non-steroidal anti-inflammatory drug (NSAID) use according to Lanas and Scarpignato (2006:136); however, NSAID-induced damage to the distal GI (gastro-intestinal) tract is also common and more frequent than previously recognised. Smale *et al.* (2001:727) concur with Lanas and Scarpignato (2006:136) that these untoward effects include increased mucosal permeability, mucosal inflammation, anaemia and occult blood-loss, malabsorption, protein loss, ileal dysfunction, diarrhoea, mucosal ulceration, strictures due to diaphragm disease as well as active bleeding and perforation. According to Gibbon (2005:348), all NSAIDs have been linked with adverse gastro-intestinal, renal, dermatological, hepatic, haematological, immunological and neurological effects. However, Lanas and Scarpignato (2006:136) also state that studies with selective COX-2 inhibitors (that include Coxibs) have shown that these agents do not increase mucosal permeability in the short term and display a reduced incidence (50 %) of serious lower GI side-effects compared to traditional NSAIDs.

Sturkenboom *et al.* (2002:132) pointed out that medical interventions for upper gastro-intestinal disorders following NSAID treatment include prescriptions for gastro-protective drugs,

hospitalisations and outpatient diagnostic procedures. They also found that the cost of medical interventions for gastro-intestinal events added 58 % to the cost of NSAID therapy. The iatrogenic costs were generated by 12.4 % of the patients, 77 % of whom had a positive history of gastro-intestinal disorders and 82 % of whom were older than 50 years. Co-prescriptions for gastro-protective drugs accounted for 78.6 % of the overall iatrogenic costs (Sturkenboon *et al.*, 2002:132).

In a study as done by Tibble *et al.* (1998:509) it was revealed that long-term NSAID ingestion is associated with mild malabsorption and that the different formulations of intestinal absorption/permeability tests vary in their sensitivity to detect the effects of NSAIDs on the small intestine. Sequential studies performed by Tibble *et al.* (1998:509) on patients receiving NSAIDs show that ingestion of the drugs lead to intestinal inflammation. The prevalence and intensity of the inflammation associated with different NSAIDs, apart from nabumetone and aspirin, are comparable.

The main factor that limits the use of traditional NSAIDs is their gastro-intestinal (GI) toxicity. Long-term use of NSAIDs is associated with dyspepsia, abdominal pain, and sometimes with gastric or duodenal perforation or bleeding. NSAID-associated serious upper GI-adverse events result in 103 000 hospitalisations and 165 000 deaths per year in the United States (Bombardier, 2002:4). Lower gastro-intestinal bleeding and perforation are more common complications than previously recognised, and represent at least one third of all gastro-intestinal complications observed with NSAID use. Studies with selective COX-2 inhibitors (that include Coxibs) have shown that, in the short term, these agents do not increase mucosal permeability or induce anaemia due to occult bleeding and that, when compared to dual COX inhibitors, lower gastro-intestinal complications may be reduced by 50 % (Lanas *et al.*, 2003:2254).

According to Mayhew (2007:341), NSAIDs have other adverse effects that are not related to the GI tract, such as nephrotoxicity and hepatotoxicity. Mayhew (2007:341) also states that these drugs all have the ability to cause fluid retention which may in turn lead to oedema. Wells *et al.* (2003:13) concur that NSAIDs may cause renal complications, hepatitis, hypersensitivity reactions, rash, and central nervous system complaints of drowsiness, dizziness, headaches, depression, confusion and tinnitus. All non-specific NSAIDs inhibit COX-1 dependent tromboxane production in platelets, thereby increasing bleeding risk. According to Wells *et al.*

(2003:133) NSAIDs should also be avoided in late pregnancy because of the risk of premature closure of the ductus arteriosus. Nausea, dyspepsia, anorexia, abdominal pain, flatulence and diarrhoea are considered minor complaints and occur in 10 % to 60 % of patients (Wells *et al.*, 2003:13).

Table 2.4 Complications and deaths attributed to gastro-intestinal (GI) events and NSAID/aspirin use taken from Lanas *et al.* (2005:1688).

Type of event	**All events (whole country)**		**Events attributed to NSAID/aspirin use (whole country)**	
	Study 1*	**Study 2**	**Study 1**	**Study 2**
All GI events	41,409	50,114	15,031	18,191
Upper GI tract: all events	35,009	43,581	12,708	15,819
Lower GI tract: bleeding events	5,330	5,478	1,935	1,992
GI perforation	1,070	1,055	388	320
Upper GI tract: deaths from all events	1,778	2,270	645	824
Lower GI tract: deaths from bleeding	284	226	103	82
Deaths from GI perforation	305	320	111	116
All deaths	2,368	2,816	860	1,022

* estimated for whole country on a population figure of 40,850,540

Tables 2.4 and 2.5 show the results from a study by Lanas *et al.* (2005:1688) based on actual count of deaths of two data sets of 2001 in Spain. The first study (study 1) was carried out in 26 general hospitals serving more than 7 million people and the second study (study 2) used a database of 197 general hospitals. Table 2.4 indicates the deaths and GI complications for Spain for 2001, including those attributed to NSAID and/or aspirin use.

The proportion of complications and deaths attributed to NSAID or aspirin use according to Lanas *et al.* (2005:1689) was 36.3 %. Table 2.5 indicates the number of hospital days and mortality rates for specific GI complications due to NSAID use.

Table 2.5 Distribution of hospitalisation and mortality due to GI bleeding and perforation by main diagnosis taken from Lanas *et al.* (2005:1688).

Description	Percentage of all GI events	Mean hospital stay (days)	Mortality rate (%)
Gastric ulcer bleeding	21.3	8.36	3.3
Duodenal ulcer bleeding	23.1	7.53	3.5
Peptic ulcer bleeding	1.1	8.55	5.3
Gastro-jejunal ulcer	0.8	9.51	3.4
Non-bleeding peptic lesion events	13.2	6.62	1.6
Unspecified GI bleeding	27.5	7.40	9.9
GI perforation	2.1	17.40	30.3
Rectal bleeding	6.5	6.90	5.3
Small-bowel diverticuli with bleeding	0.1	11.60	8.5
Small-bowel diverticulitis with bleeding	<0.1	16.20	13.3
Colonic diverticuli with bleeding	3.5	8.60	1.1
Colonic diverticulitis with bleeding	0.8	10.50	6.8

Lanas *et al.* (2005:1689) concluded in their study that the mortality rate of both upper and lower GI events were similar with the exception that upper GI events were more common.

2.1.5.2 Drug interactions with NSAIDs

Drug-drug interactions are defined by Tatro (2004:1021) as that occurrence when the effects or pharmacokinetics of a drug are changed by prior administration or co-administration of a second drug. The table below shows the drug-drug interactions for NSAIDs.

Table 2.6 Drug-drug interactions of NSAIDs adapted from Tatro (2004:1021).

Drug	Drug	Onset	Severity	Mechanism
NSAIDs (eg. Diclofenac, piroxicam, sulindac)	Bile acid sequestrants (eg. Cholestyramine, colestipol)	Delayed	Minor	Plasma clearance of piroxicam is increased and GI absorption of NSAID is decreased
NSAIDs (eg. Ibuprofen, diclofenac, indomethacin etc.)	Biphosphonates (eg. Alendronate, etidronate etc.)	Delayed	Moderate	NSAIDs and Biphosphonates may be synergistic with respect to causing gastric ulcers
NSAIDs (eg. Diclofenac, ibuprofen, indomethacin etc.)	Histamine H_2 antagonists (eg. Cimetidine, ranitidine etc.)	Delayed	Minor	Therapeutic actions of NSAIDs may be altered – mechanism unknown
NSAIDs (eg. Diclofenac, ibuprofen, indomethacin etc.)	Probenecid	Delayed	Minor	Plasma clearance of NSAIDs is reduced via renal and biliary pathways
NSAIDs (eg. Diclofenac, ibuprofen, indomethacin etc.)	Salicylates (eg. Aspirin)	Delayed	Minor	Increased metabolism and displaced protein binding of the NSAID may be involved
NSAIDs (eg. Diclofenac)	Sucralfate	Delayed	Minor	The absorption of diclofenac may be decreased. The precise mechanism is unknown

2.1.5.3 Prevention

In view of the recent controversies surrounding the cardiovascular effects of COX-2 selective agents (including Coxibs), the number of patients who receive traditional NSAIDs is likely to increase substantially. Consequently, the number at risk for NSAID-related gastro-intestinal complications is also expected to increase. Accurate identification of those who are at high risk for NSAID-related gastro-intestinal toxicity is therefore essential (Peura & Goldkind, 2005:s7).

A retrospective observational cohort study conducted by Sturkenboom *et al.* (2003:26) in the Netherlands using data from early 1996 to mid-2002, found that only 7.9 % of NSAID users during this time period had been given a preventative therapy. Of these, 6.6 % received gastro-protective agents, and an additional 1.3 % received COX-2 inhibitors (that include Coxibs). A greater percentage of patients with one or two risk factors for upper gastro-intestinal injury received gastro-protective drugs, but well over 80 % of these patients were provided with no preventative strategy. A large treatment gap exists, despite an increase in the overall prevalence of use of gastro-protective strategies, *i.e.* from 5.1 % in 1996 to 15.9 % in 2002.

Peura and Goldkind (2005:s12) state that through both prevention strategies and risk assessment, the best prevention for harmful GI effects in patients receiving NSAIDs can be found. Peura and Goldkind (2005:s12) also state that when selecting therapeutic agents, physicians should consider recent findings that further characterise the comparative safety and efficacy profiles of acetaminophen and NSAIDs, and should discuss the potential benefits and risks of various treatments with patients. Tailoring the options to a particular patient is the challenge and ideal for those caring for patients with OA.

In July 2005 the US Food and Drug Administration (FDA) recommended labelling changes for over-the-counter (OTC) and prescription NSAIDs, that include a boxed warning highlighting the potential for not only increased risk for cardiovascular events, but also for life-threatening gastro-intestinal bleeding associated with their use (FDA, 2005).

2.1.5.4 Peptic Ulcer Disease

2.1.5.4.1. Definition

Peptic ulcer disease (PUD) according to Siepler and Smith-Scott (2004:27-3) refers to lesions in the stomach or duodenum (UGI tract) that occur due to acid and pepsin activity. Wells *et al.* (2003:314) state that ulcers differ from superficial mucosal erosions in that they extend deeper into the muscularis mucosa. The three common forms of peptic ulcers include Helicobacter-pylori-associated ulcers, non-steroid anti-inflammatory drug (NSAID)- induced ulcers, and stress-related mucosal damage (also called stress ulcers).

2.1.5.4.2 Epidemiology

According to Kurata and Haile (1984:289), there were already about four million people in the United States with active peptic ulcers in the 1980s and even then about 350,000 new cases were

being diagnosed each year. Berardi and Welage (2005:630) concur that approximately 10 % of Americans will develop PUD and that the incidence would differ with ulcer type, age, gender, and geographic location. They also stated that racial, occupational, and social variables need re-evaluation in light of differences in HP (*Helicobacter pylori*) infection rates. In the U.S. the over-all prevalence of PUD, according to Berardi and Welage (2005:630), has shifted from predominance in men to nearly comparable prevalence of duodenal ulcer (DU) and gastric ulcer (GU) in men and women, although DU emerges 20 years earlier than GU in men. These recent trends suggest a declining rate for younger men and an increasing rate for older women. Factors that may have influenced these trends include the increasing prevalence of HP (*Helicobacter pylori*) infection with age, NSAID-induced ulcers in the elderly, and declining smoking rates, especially in younger men. Stress associated with increased social, occupational, and family responsibilities may also be related to recent changes observed in the male-to-female ratio.

Post *et al.* (2006:1592), state that in the Netherlands there have been a noticeable decrease in reported hospitalisation and mortality rates for peptic ulcers although admission rates for complicated ulcers remained unchanged and even increased among women. Berardi and Welage (2005:630) concur that this decline in the incidence of PUD has been ongoing since 1960, and resulted primarily from a reduction in hospital admissions for uncomplicated DU, with a less dramatic decrease in gastric ulcer (GU). In the USA (El-Serag & Sonnenberg, 1998:329), hospital admission rates between 1970 and 1995 showed a decline, the decline being far more pronounced in duodenal than gastric ulcer.

Berardi and Welage (2005:630), also state that mortality rates from PUD has declined among persons of all ages, but declining death-rates for men are in contrast to increasing rates for women. Despite these changes, PUD is one of the most common GI diseases resulting in work loss, disability, and high-cost medical care. According to the Center for Disease Control (2005), 25 million Americans will suffer from an ulcer at some point during their lifetime.

2.1.5.4.3 Pathophysiology

Chronic NSAID (including aspirin) use is clearly linked to hemorrhagic gastric erosions, GUs, (and less commonly) DUs. NSAIDs cause gastro duodenal damage by two mechanisms: firstly a direct or topical irritation of the epithelium, and secondly a systemic inhibition of endogenous gastro-intestinal (GI) mucosal prostaglandin synthesis (Wells *et al.*, 2003:314).

According to Wells *et al.* (2003:314), the association between corticosteroids alone and PUD remains controversial. However, patients receiving glucocorticoids and NSAIDs simultaneously are at increased risk of GI events.

Wells *et al.* (2003:314) also state that cigarette smoke increases ulcer risk, and the risk is proportional to the amount smoked per day. Smoking also impairs ulcer healing and promotes recurrence.

2.1.5.4.4 Mucosal protection

It is stated by Berardi and Welage (2005:633), that several mechanisms protect the GI mucosa from endogenous and exogenous noxious substances. These protective mechanisms consist of mucus secretion, bicarbonate secretion, mucosal blood flow, epithelial cell restitution, growth and wound healing after injury. It has been stated that the maintenance of mucosal integrity, by mechanisms independent of acid inhibition, is mediated by the production of endogenous prostaglandins (PGs).

2.1.5.4.5 Potential risk factors

- *Genetic factors*

  According to Berardi (1997:703) a number of genetic factors have been proposed to explain familial aggregation of PUD in patients, but some controversy still exists.

- *Gender factors*

  According to Hawkey *et al.* (2002:347), a total of 150 of 518 men (29 %) had a duodenal ulcer compared with 154 of 938 women (16 %). Hawkey *et al.* (2002:347), concluded that duodenal ulcers were more common in men than women in *H pylori* negative (22 % *v* 13 %) as well as *H pylori* positive (35 % *v* 21 %) patients.

- *Age*

  Hawkey *et al.* (2002:347), found that patients aged 60 years and older were significantly more likely to have an ulcer than erosions compared with those under the age of 60, although the difference was not large (67 % *vs.* 62 %). Patients older than 60 years were more likely to

have a gastric ulcer (71 % of ulcers) than a duodenal ulcer (29 % of ulcers) compared with those under 60 years (64 % gastric ulcer, 36 % duodenal ulcer).

- *Helicobacter pylori (H. pylori)*

Huang *et al.* (2002:14) found that uncomplicated peptic ulcer disease was significantly more common in patients positive, than those negative for *H. pylori* (41.7 % *vs.* 25.9 %). However, Hawkey *et al.* (2002:347) states that despite the association with *H. pylori*, 43 % of all duodenal ulcers occurred in patients not infected with *H. pylori*.

- *Peptic ulcer history*

According to Hawkey *et al.* (2002:347), patients with a peptic ulcer history were more probable to have an ulcer than multiple erosions. Among those with ulcers, those with a past ulcer history were more likely to have a duodenal ulcer (40.8 % of ulcers *vs.* 28.1 % of ulcers in those without a past ulcer history)

- *Cigarette smoking*

Cigarette smoking, according to Berardi and Welage (2005:632), increases the risk for the development and recurrence for DU and GU and the risk appears to be proportional to the amount smoked. The threshold for measurable risk seems to be about one-half pack (10 cigarettes) per day.

- *Psychological stress*

Clinical evaluation supports the belief that ulcer patients are adversely affected by stressful life events, however, controlled studies have failed to document a cause-and-effect relationship. Alternatively Berardi and Welage (2005:632) state that psychological factors may predispose selected patients to PUD or alter inflammatory response or resistance to HP infection.

- *Dietary factors*

Berardi and Welage (2005:632) state that items such as coffee, tea, cola beverages, beer, milk and spices may cause dyspepsia, but do not increase the risk for PUD. In addition, beverage restrictions and bland diets do not alter the frequency of ulcer recurrence. Although caffeine is a gastric acid stimulant, other constituents in decaffeinated coffee/tea, caffeine free carbonated beverages, beer, and wine are responsible for increasing gastric acid. Ethanol in high concentrations, is associated with acute gastric mucosal damage and upper

GI bleeding; however, there is insufficient evidence to confirm that ethanol causes ulcers. Stermer (2002:200) also states that low alcohol doses speed up gastric emptying, while high doses delay emptying and slow bowel motility.

According to Griffin and Scheiman (2001:33s), among NSAID users with more than one risk factor for ulcer complication, the incidence of serious complications may be as high as 4 % to 8 % per year, and for elderly NSAID users, fatal complications are close to 1 per 1000 person-years of NSAID use, and even higher for those with additional risk factors (such as prior history of ulcer disease).

2.1.5.4.6 Desired outcome

Wells *et al.* (2003:316) state that the goals of treatment of PUD are relieving the pain associated with the ulcer, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. In *H. pylori*- positive patients the goals are to eradicate the organism (Berardi & Welage, 2005:632) and cure the disease with a cost-effective drug regimen.

2.1.5.4.7 Clinical presentation

Epigastric pain is the classic and most frequent symptom of DU and GU. The pain can be described as burning, gnawing or aching and can present as a vague discomfort, abdominal fullness, or cramping. Many patients with DU describe a typical nocturnal pain that awakens them at night (Siepler & Smith-Scott, 2004:27-6). Pain related to DU often occurs a few hours after a meal, when the stomach is empty, and is usually relieved by food, but this is variable. In GU food may precipitate ulcer pain. Antacid ingestion usually provides immediate pain relief in most patients with either DU or GU.

Table 2.7 indicates that both gastric and duodenal ulcers have severe pain that can be relieved by antacids. However, gastric ulcers is associated with severe nausea and vomiting while epigastric pain and greater ulcer recurrence is more common with peptic ulcer.

Table 2.7 Prevalence of symptoms with gastric- and duodenal ulcers (Berardi, 1997:704).

Feature	**Prevalence with Gastric Ulcer**	**Prevalence with Duodenal ulcer**
Pain	++++	++++
- Epigastric	+++	++++
- Frequently severe	+++	+++
- Radiation to back	++	++
- Episodic (clusters)	+	+++
- Nocturnal	+++	++++
- Within 30 min of food	++	+
- Food relief	++	+++
- Relief by antacids	++++	++++
Anorexia	+++	++
Weight loss	+++	++
Nausea	++++	+++
Vomiting	++++	+++
Heartburn	+	+++
Bloating	+++	+++
Belching	+++	+++
Ulcer recurrence	+++	++++

Consistent (++++); Frequent (+++); Infrequent (++); Rare (+).

2.1.5.4.8 Prevention of NSAID-associated ulcer

Current options include the following:

- Proton-pump inhibitors (PPIs) are better than standard dose H_2–receptor antagonists (H_2RAs) but, not better than misoprostol in the prevention of gastric ulcer
- The efficacy of PPIs is affected by the proportion of patients infected with *Helicobacter pylori*
- High dose of H_2RAs gives only a slight reduction in the risk of gastric ulcer

(Chan & Leung, 2002:936)

2.1.5.4.9 Pharmacologic treatment

The treatment of PUD is traditionally aimed at relieving ulcer pain, accelerating ulcer healing, minimising ulcer recurrence, and reducing ulcer-related complications (Berardi & Welage, 2005:636). Wells *et al.* (2003:319) state that treatment should be initiated with PPI-based three-drug regimens, as they are most effective, better tolerated, simpler, and associated with better adherence. A 14-day course is preferred over 10 days because the longer duration favours successful eradication. However, GU healing does not correlate as strongly with acid suppression and a longer period of treatment is often necessary to heal GUs (the average ulcer size is larger than a DU).

Once full-dose anti-ulcer medication is stopped, 50-90 % of patients develop a recurrent ulcer within one year. Effective maintenance therapy reduces the recurrence rate of symptomatic DU by 20-40 %. Patients with complicated ulcers (e.g., upper GI bleeding, obstruction, perforation, or penetration) often require endoscopic or surgical treatment (Wells *et al.* 2003:273).

El-Serag *et al.* (2002:2106) concluded that the risk of clinical UGI events in NSAID users depends on their baseline risk, the additional risk associated with the individual NSAID, and the protection given by co-therapy

Table 2.8 Costs associated with NSAID treatment and upper gastro-intestinal (UGI) events adapted from El-Serag *et al.* (2002:2106).

Treatment strategy	**Frequency of use**	**Cost in 1 year, (US $)**
800mg of Ibuprofen	3 times/day	239
375mg Naproxen	2 times/day	654
Proton-pump inhibitor (30mg lansoprazole)	1 time/day	1393
200µg Misoprostol	3 times/day	970
Coxib (100mg Celecoxib)	2 times/day	1029
Helicobacter pylori treatment*		82+71=153
Cost of clinical UGI event		28000
Helicobacter pylori serologic analysis		20

* Helicobacter pylori treatment consists of bismuth subsalicylate / metronidazole / tetracycline combination plus proton-pump inhibitor therapy (e.g. omeprazole 40mg twice daily plus bismuth subsalicylate 525mg four times daily plus metronidazole 250-500mg four times daily plus tetracycline 500mg four times daily).

2.1.5.5 Lower gastro-intestinal (GI) damage

The gastro-duodenal toxicity of conventional non-steroidal anti-inflammatory drugs (NSAIDs), according to Lanas and Scarpignato (2006:136), is widely recognised and side-effects involving the more distal portions of the intestinal tract are less ordinary and frequently underestimated. Thiefin and Beaugerie (2005:287) state that it is now well recognised that NSAID-induced toxicity extends not only to the stomach and proximal duodenum but rather to the entire gastro-intestinal tract as well as the small bowel, colon and rectum.

Long-term NSAID therapy usually causes clinically silent enteropathy characterised by increased intestinal permeability and inflammation. Chronic occult bleeding and protein loss may result in iron-deficiency anaemia and hypoalbunemia (Thiefin & Beaugerie, 2005:289).

According to Adebayo and Bjarnason (2006:186), the short-term and long-term damage of NSAIDs on the small bowel (NSAID enteropathy) is more frequent than NSAID gastropathy.

Furthermore, NSAID enteropathy is associated with complications (bleeding and protein loss). While many of these are mild, the severe events (significant bleeding, perforation, obstruction, and sudden death) are as frequent as those reported for NSAID gastropathy.

The incidence of NSAID-associated lower GI-side effects, according to Lanas and Scarpignato (2006:136), may exceed that detected in the upper GI tract and include a wide spectrum of lesions. In addition, the frequency of life-threatening complications due to the lower GI tract represents nowadays no less than a third of all GI complications associated with the use of these agents.

NSAIDs can also induce small-bowel ulcers that, according to Thiefin and Beaugerie (2005:287), may occasionally lead to acute bleeding, perforation, or chronic scarring responsible for diaphragm-like strictures. At the colon and rectum, NSAID use can result in *de novo* lesions such as non-specific colitis and rectitis, ulcers, and diaphragm-like strictures. NSAIDs have also been implicated in the development of segmental ischemic colitis. In patients with diverticular disease, NSAID use increases the risk of severe diverticular infection and perforation, and can trigger exacerbations of ulcerative colitis or Crohn's disease. Thiefin and Beaugerie (2005:290) also found that colonic toxicity is more common with sustained release formulations, which result in higher NSAID levels in contact with the proximal colonic mucosa, while NSAID rectal suppositories can cause local lesions. These lesions may develop, either in the healthy gut (Thiefin & Beaugerie, 2005:286) or at sites of pre-existing bowel disease, and in some cases NSAID therapy may expose previously undiagnosed bowel disease. Many adverse events involving the lower intestine have been reported, some of them being potentially life threatening.

According to Lanas and Scarpignato (2006:139), investigations have revealed that intestinal inflammation could be present in up to 60-70 % of patients taking NSAIDs and that, once established, it may be detected up to 1-3 years after the NSAID had been stopped. Davies *et al.* (2000:137) state that current prevention strategies that lessen the extent of damage in the upper GI tract are not effective in the lower GI tract. Only therapy with selective COX-2 inhibitors (that include Coxibs) may represent an alternative when the intestine is the target for prevention. However, long-term therapy with this class of drug may show severe cardiovascular (CV) risk factors.

Thiefin and Beaugerie (2005:287) and Davies *et al.* (2000:137) list the following outcomes of intestinal toxicity during NSAID-therapy:

- **Small bowel area**

Clinically silent enteropathy

- Increased intestinal permeability
- Intestinal inflammation
- Malabsorption of bile salts, d-xylose and fat

Enteropathy with clinical manifestations

- Exudative enteropathy: hypoalbunemia
- Ulcers of the small bowel
- Occult bleeding: chronic iron-deficiency anaemia
- Acute events: perforation, bleeding
- Scarring: diaphragm-like strictures
- Villous atrophy

- **Colon and rectum area**
  - Non-specific *de novo* colitis
  - Colonic ulcers
  - Diaphragm-like strictures of the colon
  - Rectitis and complications (stenosis, perforation, fistulas)
  - Eosinophilic colitis
  - Segmental ischemic colitis
  - Severe complications of diverticular disease: perforation, bleeding
  - Flare of Crohn's disease
  - Flare of ulcerative colitis

2.1.6 SELECTIVE COX-INHIBITORS

2.1.6.1 Introduction

It has been concluded that there are two COX isoforms, identified as COX-1 and COX-2. The structure of these isoforms, according to Bombardier (2002:3), are very similar, the difference being a single amino acid enabling the design of selective COX-2 drugs.

COX pathway inhibitors include aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) including COX-inhibitors, selective COX-2 inhibitors and specific cyclo-oxygenase-2 inhibitors (Coxibs). Aspirin irreversibly inhibits platelet COX-1 and consequent production of TXA (a potent platelet activator and vasoconstrictor). Although aspirin has demonstrated value as an analgesic, anti-inflammatory, and anti-trombotic agent, it is also associated with major gastro toxicity due to the inhibition of the gastro-protective COX-1 function (Bombardier, 2002:4).

Clinical experience with agents that may prevent or treat distal tract damage is very limited according to Lanas *et al.* (2003:2253), and from this perspective, selective COX-2 inhibitors (which include Coxibs) may be the drugs of choice in the high-risk patient that needs NSAIDs. Another important area of uncertainty is the impact of NSAID use in patients with inflammatory bowel diseases. In a study conducted by Lanas *et al.* (2003:2253) data from animal models suggested that inhibition of both COX-1 and COX-2 derived prostaglandins affect the severity of mucosal inflammation. However, current epidemiological and clinical data are contradictory. Since many patients with inflammatory bowel diseases need NSAID treatment, clinicians should be aware of potential problems and try to minimise or reduce NSAID exposure. Lanas *et al.* (2003:2253) concluded that further studies are needed to define the effect of both non-selective NSAIDs and selective COX-2 inhibitors in these patients.

With selective COX-2 inhibitors (which include Coxibs), Thiefin and Beaugerie (2005:286) found that the risk of gastro-intestinal toxicity was less than that of conventional NSAIDs but was not entirely eliminated. Their experimental studies also suggested that long-term COX-2 inhibitor therapy may cause damage to the previously healthy small bowel, and similar to conventional NSAIDs, COX-2 inhibitors that may be able to trigger exacerbations of inflammatory bowel disease.

2.1.6.2 COX-2 hypothesis

The COX-2 hypothesis proposes that selective COX-2 inhibitors (including Coxibs) would be as effective as traditional NSAIDs at comparable inhibitory doses, while sparing the GI mucosa (Patrono *et al.*, 2001:9).

Based on the results of controlled clinical trials, the US Food and Drug Administration (FDA) approved celecoxib and rofecoxib for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, the management of acute pain in adults, the treatment of primary dysmenhorrea, and the reduction of the number of adenomatous colorectal polyps in familial adenomatous polyposis (Bombardier, 2002:5). Another Coxib, valdecoxib was also approved by the FDA for treatment of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis, as well as the treatment of pain associated with menstrual cramping. In a study done by Silverstein *et al.* (2000:1253) it was determined that celecoxib, a specific cyclo-oxygenase-2 inhibitor (Coxib), when used for 6 months in a dosage of two to four times the maximum therapeutic dosage, is associated with a lower incidence of combined clinical upper GI events than comparator NSAIDs (ibuprofen and diclofenac) used at standard therapeutic dosages.

Endoscopic studies performed by Laine *et al.* (1999:776) demonstrate that coxibs, which have no inhibitory effect on COX-1, have a similar effect as placebo on the gastro duodenal mucosa. A 6-month, double-blind, randomised, controlled trial compared the incidence of endoscopic gastro duodenal ulcers in patients with osteoarthritis assigned to rofecoxib (25 or 50mg/day), ibuprofen (800mg tid), or placebo. At 12 weeks, 85 % fewer endoscopic ulcers ≥3mm were seen with 25mg/day rofecoxib and 74 % fewer with 50-mg/day rofecoxib compared with ibuprofen. These results confirm the GI-sparing effect of rofecoxib in a study using endoscopic gastro duodenal ulcers as the endpoint (Laine *et al.*, 1999:776).

The GI safety of celecoxib (100mg, 200mg, or 400mg bid) compared to naproxen (500mg bid) and placebo was analysed in a separate study including patients with rheumatoid arthritis (Simon *et al.* 1999:1926). The incidences of the most frequently reported GI tract adverse events (dyspepsia, diarrhoea, abdominal pain, nausea, and flatulence) combined were 19 % for placebo; 28 % for 100 mg, 25 % for 200 mg, and 26 % for 400 mg of celecoxib twice daily; and 31 % for naproxen. Celecoxib demonstrated anti-inflammatory and analgesic efficacy comparable with naproxen, but with a significantly lower incidence of gastroduodenal ulceration than naproxen, and not significantly different from placebo.

In conclusion, these results of endoscopic studies provide clinical evidence for the improved GI safety of coxibs compared with NSAIDs (Simon *et al.* 1999:1927), and thus concur with the COX-2 hypothesis.

2.1.6.3 Effectivity

In a study performed by Sigthorsson *et al.* (2000:527) patients were treated for one week with indomethacin 50mg three times daily, and showed significantly increased intestinal permeability compared with placebo, while treatment with rofecoxib 25mg or 50mg daily did not. The absence of a significant effect of rofecoxib on intestinal permeability at doses at least twice those recommended to treat osteoarthritis is, according to Sigthorsson *et al.* (2000:527), consistent with other studies that have demonstrated little or no injury to the gastro-intestinal mucosa associated with rofecoxib therapy.

According to Bombardier *et al.* (2000:1520), rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a nine month median follow-up, approximately two confirmed GI events per 100 patient-years [the number of patients multiplied by the duration of the follow-up (Gallant, 2005)] occurred with rofecoxib, as compared with between four and five GI events per 100 patient-years with naproxen. The respective rates of complicated and confirmed events (perforation, obstruction, and severe upper gastro-intestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years. The incidence of myocardial infarction as evaluated by Bombardier *et al.* (2000:1523) was lower among patients in the naproxen group than among those in the rofecoxib group. However, the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups. Bombardier *et al.* (2000:1525) thus concluded that when treating patients suffering from rheumatoid arthritis with rofecoxib (a specific cyclo-oxygenase-2 inhibitor) the patients suffered from fewer clinically important upper gastro-intestinal events than when treated with naproxen (a non-selective inhibitor).

Although similar in design, Bombardier (2002:8) found that CLASS (Celecoxib Long-term Arthritis Safety Study) and VIGOR (Vioxx® Gastro-intestinal Outcomes Research) were not entirely comparable. The most significant differences were:

- between study populations - with osteoarthritis and rheumatoid arthritis in CLASS and with only rheumatoid arthritis in VIGOR;
- with use of cardio-protective therapy - aspirin was used in CLASS but not in VIGOR;

- with comparator NSAIDs - ibuprofen and diclofenac were used in CLASS and naproxen was used in VIGOR;
- with study designs that differed with respect to endpoint definitions and methods of recording events - such as bleeding, which was more broadly defined in the VIGOR trial than in the CLASS trial;
- with study protocols - the investigators in the VIGOR trial could make decisions whether to perform diagnostic tests on patients suspected to have GI events, whereas in the CLASS trial the study protocol encouraged endoscopic procedures, differences that may have led to the recording of more transient, clinically less important ulcers in the CLASS trial.

The results of the CLASS study were less robust than expected, which may be explained by study design, relatively high levels of aspirin use, high rates of discontinuation, drug-specific factors (lower COX-2 selectivity), or a combination of these elements (Bombardier, 2002:8).

2.1.6.4 Coxib withdrawal from the pharmaceutical market

Merck & Co. announced a voluntary withdrawal of Vioxx® (rofecoxib) products on 30 September 2004. The company's decision, which was effective immediately, was based on, three-year data from a prospective, randomised, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on Vioxx®) trial (Merck, 2004).

The trial was designed to evaluate the efficacy of Vioxx® 25mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study there was an increased relative risk for cardiovascular events, such as heart attack and stroke, commencing after 18 months of treatment in the patients taking Vioxx® compared to those taking placebo. Thus the results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on Vioxx®, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labelling for Vioxx® (Merck, 2004).

On April 7, 2005, less than a year after the withdrawal of Vioxx® from the market, Pfizer was asked to voluntarily withdraw Bextra® (valdecoxib) from the U.S. market on recommendation by the FDA (FDA, 2005), citing an increased risk of cardiovascular events (such as heart attack, stroke and death) also the risk of serious, sometimes fatal, skin reactions such as Stevens-Johnson syndrome and erythema multiforme (FDA, 2005).

Pfizer first acknowledged cardiovascular risks associated with Bextra® in Noverber of 2004 when they submitted the results of a then recently completed study to the FDA (FDA, 2005). The report indicated patients using Bextra® (valdecoxib) while recovering from heart surgery were two times more likely to suffer a stroke or heart attack than those taking placebos.

Shortly after the withdrawal of Bextra® in April 2005, the European Commission withdrew the marketing authorisation for Rayzon® on 24 June 2005, following the notification by the marketing authorisation holder (Pharmacia Europe EEIG) on 21 June 2005 to voluntarily withdraw Rayzon® (indicated for the short-term treatment of post-operative pain) as there are no plans to market this product in future (Wathion, 2005).

Prexige® (lumiracoxib), a Coxib for the treatment of osteoarthritis, was also withdrawn from the market (on 11 August 2007) in accordance with the decision of the Therapeutic Goods Administration (TGA) to withdraw all doses of Prexige® due to a number of cases of serious liver side-effects in patients taking Prexige® (Novartis, 2007). This was announced by Novartis Pharmaceuticals on 11 August 2007.

Celebrex®, Rayzon® (Anon., 2008a:51), and Arcoxia® (South Africa, 2007:6) are the only coxibs still available in South Africa. Rayzon® (MCC, 2004:4) was registered with the Medicines Control Council (MCC) in 2004 and Arcoxia® (South Africa, 2007:3) was registered with the MCC in 2007, even though the FDA did not approve Arcoxia® (FDA, 2005) for marketing in the US, and the European Commission withdrew marketing authorisation for Rayzon® in 2005 (Wathion, 2005). (Note that the registration of Arcoxia® is not within the scope of the time period of this study.)

The results of clinical studies of one molecule in a given class is not necessarily applicable to others in the same class. Therefore, the long-term use of other drugs in the class, consisting of specific cyclo-oxygenase-2 inhibitors and NSAIDs, is unknown (Merck, 2004). According to Fields *et al.* (2005), the FDA decided that the benefits of Celebrex® exceeded the risk and that it could remain on the market. This was consistent with the overwhelmingly positive vote by the FDA Advisory panel to keep this medication available. Celebrex® will, however, require the "black box" warning to be placed on its package insert. Regarding Vioxx®, which Merck had previously voluntarily removed from the market, the FDA noted that in order for the drug to return to the market, it would first be required that a supplemental new drug application be filed and be subjected to public review.

2.1.6.5 Coxibs vs. combination NSAID and proton-pump inhibitor (PPI) therapy

According to Spiegel *et al.* (2006:27) dyspeptic symptoms are far more common than ulcer complications in users of non-steroidal anti-inflammatory drugs (NSAIDs), and economic models indicate that dyspepsia rates (not ulcer complications) are the main determinant of cost-effectiveness in treating arthritis.

Spiegel *et al.* (2006:30) performed a meta-analysis to compare rates of dyspepsia for two common therapies in high-risk patients with arthritis: specific cyclo-oxygenase-2 inhibitor (Coxib) alone and combination therapy with a non-selective NSAID and a proton-pump inhibitor (PPI) (NSAID plus PPI). The meta-analysis of 26 studies comparing dyspepsia between Coxibs and NSAIDs revealed a 12 % relative risk reduction for Coxibs with an absolute risk reduction of 3.7 %. The meta-analysis of four studies comparing dyspepsia between the NSAID plus PPI combination and NSAIDs alone revealed a 66 % relative risk reduction for NSAID plus PPI with an absolute risk reduction of 9 %. Compared with the NSAID strategy, the number needed to treat to prevent dyspepsia was 27 for Coxibs and 11 for NSAID plus PPI.

The analysis by Spiegel *et al.* (2006:35) concluded that NSAID plus PPI may be superior to Coxibs in minimising incident dyspeptic symptoms during the treatment of chronic conditions. Thus NSAID plus PPI therapy is preferred to Coxibs in the treatment of patients with arthritis at high risk of gastro-intestinal events, due to the high prevalence and expense of dyspeptic symptoms.

However, in a study conducted by Teeling *et al.* (2003:342) it was found that elderly patients who tended to receive more prescriptions were prescribed COX-2 inhibitors (including selective COX-2 inhibitors and Coxibs) more frequently than non-selective NSAIDs. This suggests that COX-2 inhibitors are preferred in high risk patients.

Table 2.9 Examples of daily costs of drug treatment with different NSAID strategies (Lanas, 2004:321)

Drug 1. (non-steroidal anti-inflammatory drugs, NSAID)	**Drug 2. (anti-ulcer agent) (mg/day)**	**Cost/day (€)**	**Tablet/day**
Rofecoxib 25mg/day	-	1.60	1
Rofecoxib 12.5mg/day	-	1.31	1
Celecoxib 200mg/day	-	1.35	1
Celecoxib 400mg/day (2 x 200)	-	2.70	2
Active ingredient (generic product) (mg/day)			
Diclofenac (150mg)	Omeprazole (20mg)	1.11	4
Ibuprofen (2400mg)	Omeprazole (20mg)	1.35	5
Naproxen (1000mg)	Omeprazole (20mg)	1.19	3
Aceclofenac (200mg)	Omeprazole (20mg)	1.51	3
Piroxicam (20mg)	Omeprazole (20mg)	1.08	2
Active ingredient plus minimum price of proton pump inhibitor (mg/day)			
Diclofenac (150mg)	Omeprazole (20mg)	0.5	4
Ibuprofen (2400mg)	Omeprazole (20mg)	0.74	5
Diclofenac (150mg)	Lansoprazole (30mg)	0.5	4
Ibuprofen (2400mg)	Lansoprazole (30mg)	0.5	5
Diclofenac (150mg)	Pantoprazole (40mg)	1.86	4
Ibuprofen (2400mg)	Pantoprazole (40mg)	2.1	5
Active ingredient plus maximum price of PPI or misoprostol (mg/day)			
Diclofenac (150mg)	Omeprazole (20mg)	2.24	4
Ibuprofen (2400mg)	Omeprazole (20mg)	2.81	5
Diclofenac (150mg)	Lansoprazole (30mg)	2.01	4
Ibuprofen (2400mg)	Lansoprazole (30mg)	2.25	5
Diclofenac (150mg)	Pantoprazole (40mg)	2.03	4
Ibuprofen (2400mg)	Pantoprazole (40mg)	2.27	5

Diclofenac (150mg)	Rabeprazole (20mg)	2.01	4
Ibuprofen (2400mg)	Rabeprazole (20mg)	2.25	5
Diclofenac (150mg)	Esomeprazole (20mg)	1.75	4
Ibuprofen (2400mg)	Esomeprazole (20mg)	1.99	5
Diclofenac (150mg)	Misoprostol (800mcg/day)	1.41	7
Ibuprofen (2400mg)	Misoprostol (800mcg/day)	1.65	8
Coxib plus PPI combinations (mg/day)			
Rofecoxib (25mg)	Omeprazole (20mg)	2.44	2
Rofecoxib (12.5mg)	Omeprazole (20mg)	2.15	2
Celecoxib (200mg)	Omeprazole (20mg)	2.19	2
Celecoxib (400mg)	Omeprazole (20mg)	3.54	3

The table above indicates the daily cost of drug treatment with different strategies based on prices of the first 6 months of 2003 that have been used to estimate the costs of preventing a gastro-intestinal (GI) bleeding event with the different strategies (Lanas, 2004:321).

In a study by Maetzel *et al.* (2003:289) it was found that patients with a history of a clinical UGI (upper gastro-intestinal) event, Rofecoxib alone is both less costly and more effective than Naproxen co-prescribed with a PPI. In the table above Lanas (2004:321) states that Naproxen co-prescribed with a PPI, omeprazole in this case, is less costly than Rofecoxib alone. Rofecoxib has been withdrawn from the market (Merck, 2004) but Lanas (2004:321) and Maetzel *et al.* (2003:289) agree that adding a PPI to Rofecoxib (a coxib) is not an economically attractive strategy in comparison with Rofecoxib alone, in view of the high cost utility ratios of $281.244 per QALY gained. Celecoxib alone is the most economically acceptable strategy, because the strategies that are marginally more effective (celecoxib plus PPI, diclofenac plus PPI) are not economically attractive (Maetzel *et al.*, 2003:289).

Maetzel *et al.* (2003:288) also found that for patients at average risk, rofecoxib increased costs relative to naproxen ($3,173 versus $1,576), but also minimised clinical GI events by 13 % and complicated GI events by 4.3 %. The marginal cost for each QALY gained was high, at $271,188. The use of the CLASS data generated similar results. Celecoxib increased costs relative to diclofenac and ibuprofen ($3,371 versus $1,570 versus $1,141), but reduced the absolute risk of GI events. Neither of the more effective strategies (celecoxib and diclofenac) appear to be economically attractive compared with the least costly strategy (ibuprofen). According to the Mediscor Medicine Review Celebrex® 200mg capsules (active ingredient: celecoxib) was a cost-driving product, and ranked either fourth or fifth among the top products contributing to medicine expenditure from 2004 to 2007 in South Africa (Bester, 2007:12).

2.2 ASPECTS OF PHARMACOECONOMICS AND DRUG UTILISATION REVIEW

2.2.1 HEALTH CARE

2.2.1.1 Introduction

According to Dennill *et al.* (2002:2) primary health care includes a political philosophy that supports radical changes in both the design and content of conventional health care services. It promotes an approach to health care based on principles that allow people to receive the care that enables them to lead socially and economically productive lives. According to Spilker (1996:3) the general assessment of well-being can be described as an individual's overall satisfaction with life and a general sense of personal well-being. Jefferson *et al.* (2000:17) state that in a traditional public health approach, health problems are usually evaluated by expressing their degree of occurrence (incidence and prevalence), seriousness (mortality), and overall weight (costs).

One of the aims of the South African National Drug Policy (South Africa, 1996) is to promote the rational prescribing, dispensing and use of drugs by medical, paramedical and pharmaceutical personnel and to support informed and proper use of drugs by the community. To guarantee rational prescribing the Department of Health will gather, evaluate and circulate systematic data on drug utilisation to monitor and act on policy adherence.

2.2.1.2 Health objectives

The health objectives of the National Drug Policy, as published in 1996 are as follows:

- To ensure the availability and accessibility of essential drugs to all citizens.
- To ensure the safety, efficacy and quality of drugs.
- To ensure good dispensing and prescribing practices.
- To promote the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training, education and information.
- To promote the concept of individual responsibility of health, preventative care and informed decision making.

Most of the above objectives have received the attention of the authorities and in some or other way been adapted and implemented. Pharmacoepidemiological studies can evaluate the safety, quality and efficacy of drugs used in South Africa (South Africa, 1996).

2.2.2 MANAGED HEALTH CARE (MHC)

Managed health care is a method of health care delivery bent on controlling the cost of health care, quality of health care, and access to that care. According to Powell (2000:3), managed care can be defined as a collection of techniques used by or on behalf of purchasers of health care benefits to manage and maintain health care costs by influencing patient care decision making through case-by-case evaluation of the appropriateness of care before its provision. Implementation of managed care implementation follows a string of cost control measures like insurance benefit limitations, prepaid health plans, prospective payment systems and fee schedules.

Attention is paid to MHC in a variety of ways, *inter alia*, the following:

Health maintenance organisation (HMO) – This is a type of managed care organisation (MCO) according to Kongstvedt (2004:26) that provides a form of health care insurance coverage that is fulfilled through hospitals, doctors and other providers with which the HMO has a contract (Anon., 2008b).

Preferred provider organisation (PPO) – This organisation deals with a limited number of independent providers (such as medical doctors, hospitals, and other health care providers) to obtain services for its members at a discount (Kongstvedt, 2004:10).

Case management – this is a joint process to assess, plan, implement, organise, monitor, and evaluate options and services to meet an individual's health needs through communications and available resources to promote quality and cost-effective outcomes (Powell, 2000:5).

Managed care is an ever changing dynamic force – economically driven – that is continually trying out new delivery systems. The objective of managed care (Powell, 2000:3) is to encourage consumers, providers, and payers to all become responsible for the sensible use of limited health care resources. In the RSA managed health care is mainly implemented in the private health care sector, but the principles have also been used in the past in the public health care sector (Serfontein, 2008). An example is the restricted availability of medicine through the medicine code system as well as the essential drug list (Department of Health, 2006).

2.2.3 PRESCRIBED MINIMUM BENEFITS IN THE RSA

In South Africa a package of minimum benefits was introduced, currently referred to as Prescribed Minimum Benefits. Medical schemes have to pay these from the risk benefits and not from a member's day-to-day benefits. Schemes have to cover major medical treatment for certain conditions as defined under prescribed minimum benefits. They must cover these treatments, even if there are scheme exclusions or waiting periods have been applied to a membership or a limit has been exhausted (Discovery, 2007a).

The Council for Medical schemes introduced the concept of prescribed minimum benefits in 2000 to define minimum levels of coverage (Discovery, 2007a). The prescribed minimum benefits of the Medical Schemes Act 131 of 1998 only became effective in January 2000 (Pearmain, 2000:4). Prescribed minimum benefits serve as a safety net. They make sure that members are not without care for certain major medical expenses because they cannot afford it (Discovery, 2007a). Prescribed minimum benefits are provided for in the Medical Schemes Act (131/1998).

Prescribed minimum benefits aim to do the following:

- Provide access to coverage where members do not have medical scheme coverage if they become seriously ill because their plan benefits or limits have been exceeded.
- Avoid additional pressure on the resources of public hospitals because these patients then need to be treated by the state.

- Encourage more efficient use of private and public health care resources.

(Discovery, 2007a)

Since 2004 the prescribed minimum benefits have been covering the diagnosis, medical management and medication of a specified list of chronic conditions known as the Chronic Disease List.

The Chronic Disease List is a list of 26 chronic conditions that medical schemes must cover as part of the prescribed minimum benefits. All medical schemes must provide full coverage for the diagnosis, medical management and medication for these conditions.

The Council for Medical Schemes chose these conditions based on their frequency, severity and response to treatment. The Council further published treatment algorithms for schemes to use as guidelines on how to cover medicine for the 26 conditions (Discovery, 2007a). However, of the three main diseases (rheumatoid arthritis, osteo-arthritis and peptic ulcer disease due to the relationship with NSAIDs) discussed in this chapter, only rheumatoid arthritis is included among the 26 chronic conditions on the list for prescribed minimum benefits.

According to Discovery's Chronic Illness Benefit Formulary (Discovery, 2007a) the following drugs and some of their generic products are used for the treatment of rheumatoid arthritis: diclofenac, ibuprofen, indomethacin, meloxicam, piroxicam, chloroquine, zathioprine, sulfasalazine, prednisone and folic acid.

2.2.4 PHARMACOECONOMICS

2.2.4.1 Introduction

Pharmacoeconomic studies are designed to help determine the actual cost of an intervention when all of its costs and savings are incorporated and with the best use of health care resources in mind (Cantor, 2002:s28).

Health care resources are almost always limited, and it is important to analyse new interventions from the perspective of their cost burden. In recent years pharmacologic interventions have absorbed an increasing percentage of health care dollars. Cantor (2002:s28) points out that new clinical interventions or procedures are often expensive to purchase, but the additional expense of their purchase can be justified by the savings that result from fewer adverse events, fewer surgeries, lower mortality and morbidity, improved efficacy and fewer disabilities.

2.2.4.2 Historical perspective

Two decades ago the U.S. spent $560 billion on health care according to Bootman *et al.* (1991:3), representing slightly over 11.1 per cent of the nation's gross national product at the time. Bonk (1999:8) also made an analyses of U.S. government health care expenditures (using 1980 and 1990 to predict through 2030) which showed an increasing portion of its gross domestic product (GDP) consumed by health care – roughly up to 15 %. A predicted broaching of the $US 1 trillion mark for health care expenditures by the year 2000 occurred in 1996, although with the lowest growth in expenditures (4.4 %) since 1960.

South Africa, according to the South African Medical Research Council (MRC, 2006:204), is experiencing population ageing. The prevalence of diseases such as osteoarthritis and rheumatoid arthritis (Hansen & Elliott, 2005:1685), as well as other conditions that require the use of NSAIDs, increases with age, affecting individuals in the middle to later years of life. The MRC (2006:205) estimated that the South African fertility rate has decreased from 6.1 live births per woman in the 1950s to our current level of approximately 2.5 live births per woman.

According to McCombs (1998:112s), the changing state of medical technology makes it important for medical professionals to evaluate the cost-effectiveness of new medical technologies and innovations to update and improve clinical guidelines.

2.2.4.3 Definition of pharmacoeconomics

Pharmacoeconomics has been defined as the description and analysis of the costs and consequences of drugs and drug therapy and its impact on individuals, health care systems and society (Bungay & Sanchez, 2003:26). Pharmacoeconomics addresses both economic and humanistic outcomes, and pharmacoeconomic research, according to Osterhaus and Boyer (2003:80), can provide increased confidence in health care decisions if used correctly.

2.2.4.4 General principles of analysis

The steps or principles of pharmacoeconomic analysis, according to Bonk (1999:89), focus on understanding and evaluating pharmacoeconomic research. The findings of research can be positive, neutral or negative in relation to the study's objective, and can only benefit the patient, provider, payer and public when communicated in useful formats and through effective media.

Below are the ten general principles of analysis:

- Define the problem
- State the objectives
- Identify alternatives
- Analyse benefits/ effectiveness
- Analyse the costs
- Differentiate perspective of analysis
- Perform discounting
- Analyse uncertainties
- Address ethical issues
- Interpret the results

(Osterhaus & Boyer, 2003:80)

2.2.4.5 Pharmacoeconomic methodologies

By definition pharmacoeconomic evaluations include any study designed to asses the costs (i.e. resources consumed) and consequences of alternative therapies. This includes such methodologies labelled as cost-benefit, cost-utility and cost-effectiveness.

2.2.4.5.1 Cost-benefit analysis

According to Bungay and Sanchez (2003:32), in a cost-benefit analysis (CBA), the benefits acquired from a programme or intervention, and all the costs of providing that programme or intervention are identified and converted into equivalent dollars in the year in which they will occur. CBA, according to Strom and Kimmel (2006:474), compares the cost of an intervention to its benefits, and measures both costs and benefits in the same monetary units (e.g. dollars), in the year in which they will occur, across programmes and even outside health care (Jefferson *et al.* 2000:13). Results of these analyses can be expressed either as a cost-benefit ratio, or a net cost or benefit (Bungay & Sanchez, 2003:32). CBA assesses whether the outcomes (benefits) outweigh the inputs (costs) of a programme or intervention (Barner & Rascati, 2003:115). According to economic theory, the consequences of a programme should be measured as the willingness of the individuals who bear those consequences to pay (Barner & Rascati, 2003:115).

Bonk (1999:29) adds that cost-benefit analysis, unlike cost-of-illness analysis, assesses both the inputs (costs) of a disease along with the outputs (benefits) of a treatment or treatments. Costs in this regard reflect expenditures on the disease and the treatment; benefits quantify the outcomes of the treatment.

- In a study done by Belisari and Mantovani (2001:54), the costs of NSAIDs in managing GI lesions were considered. A cost-benefit analysis was performed where the effect was expressed as net cost or benefit consequent to the use of Amtolmetin-Guacil (AMG) *vs* other NSAIDs. Belisari and Mantovani (2001:54) concluded that the number and more desirable spectrum of GI lesions occurring in patients treated with AMG compared with other NSAIDs indicated a potentially dramatic reduction in costs. This reduction, according to their findings, outweighs the higher acquisition price of AMG, therefore showing it to have a favourable economic profile.

- The American college of gastroenterology (ACG) also conducted a cost-benefit analysis comparing the burden of cost from hospitalisation for NSAID-related GI bleeding, to using PPIs to help protect against serious potential injury to the GI tract (ACG, 2007:2). The ACG (2007:2) reviewed prescription records for the veterans administration (VA) medical system and Medicare, with an overall population of almost half a million veterans. The ACG (2007:2) found that half of those with GI bleeding events were hospitalised. One third of patients with GI bleeding events were prescribed a PPI, and were 60 % less likely to be hospitalised. Their overall median total medical costs were significantly lower than patients who were not prescribed a PPI. However, these finding also suggest that reduced hospitalisation costs offset higher pharmacy costs (ACG, 2007:2).

2.2.4.5.2 Cost-effectiveness analysis

Strom and Kimmel (2006:474) state that cost-effectiveness analysis compares the cost of a medical intervention to its effectiveness, and that costs are determined in monetary units (e.g. dollars), while effectiveness is determined independently and may be measured in terms of any clinically meaningful unit (e.g., life years extended). Decisions are then based on the effectiveness to cost ratios between the competing programmes. Jefferson *et al.* (2000:12) state that when the outcomes of different interventions vary but can be measured in identical natural

units, then inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.

$$CER = \frac{Cost_{nt} - Cost_{cst}}{Effectiveness_{nt} - Effectiveness_{cst}}$$

Where CER = cost - effectiveness ratio

$Cost_{nt}$ = cost of the new treatment

$Cost_{cst}$ = cost of the treatment standard

$Effectiveness_{nt}$ = effectiveness of the new treatment

$Effectiveness_{cst}$ = effectiveness of the current standard of treatment

(Carroll, 1998 : 256)

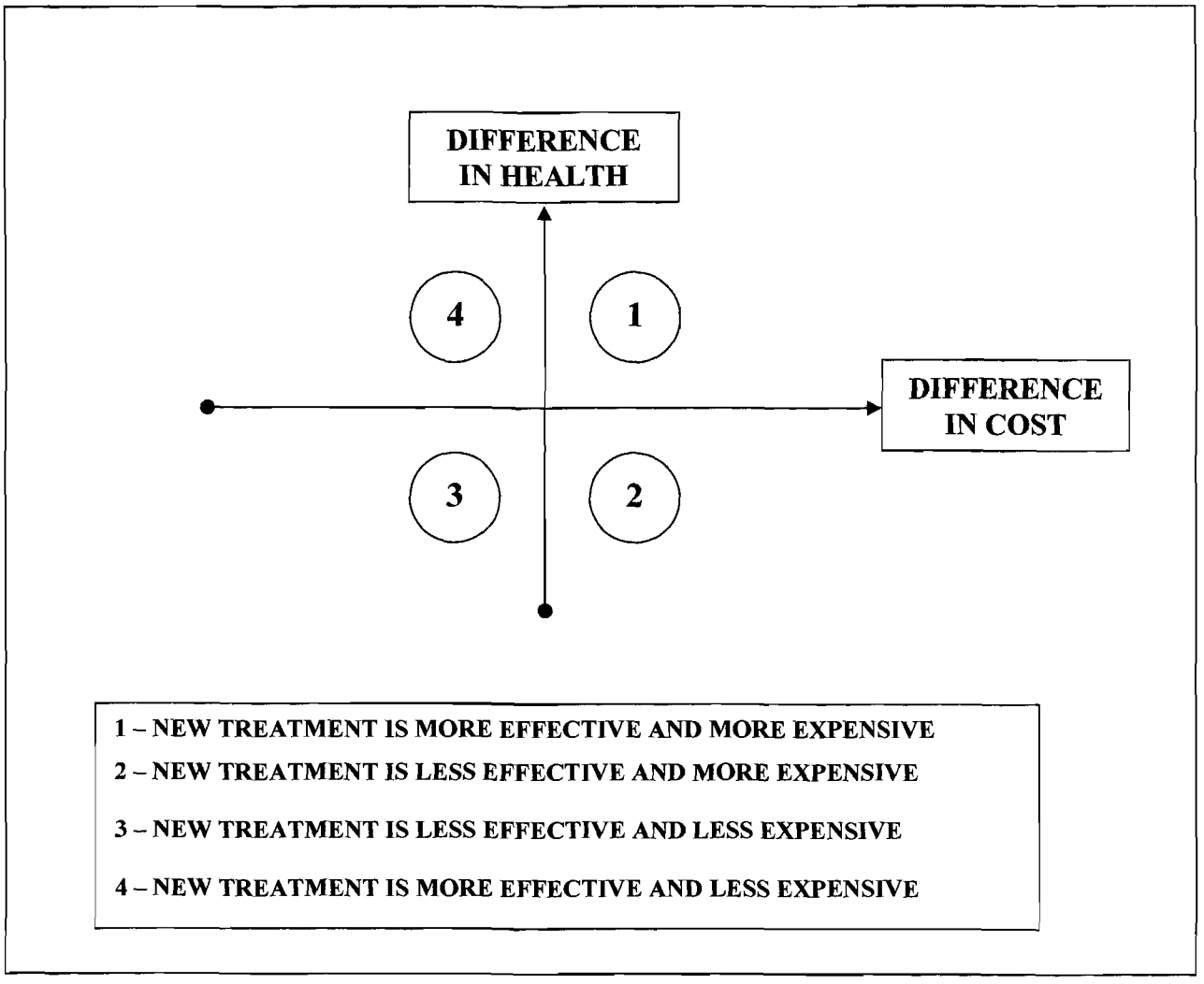

Figure 2.3. The four possible qualitative results in a cost-effective analysis (CEA), adapted from Lara *et al.* (2004:112)

An adequate cost-effectiveness analysis (CEA), as stated by Kreling and Mott (1993:415) is defined as one that uses various methods to measure and evaluate patterns of drug use, and/or efforts to alter drug use. CEA also performs an analysis of the costs of the review or intervention methods employed, with a focus on efficiency.

2.2.4.5.3 Cost-minimisation analysis

Bungay and Sanchez (2003:32) state that cost-minimisation analysis can be used to compare two or more treatment alternatives that are equal in efficacy, and treatment alternatives are measured in monetary terms (e.g. dollars). The aim is to decide the cheapest way of achieving the same outcome (Jefferson *et al.*, 2000:12). An example of this type of analysis with regard to drug therapy may be the evaluation of two generically alike drugs in which the outcome has been proved to be equal; though, the purchase and administration costs of the two drugs may be significantly different.

2.2.4.5.4 Cost-utility analysis

Cost-utility analysis, according to (Bungay & Sanchez, 2003:33), is an economic tool in which the intervention or costs of a treatment alternative are expressed in monetary terms and outcomes or consequences are expressed in terms of patient preference or quality-adjusted-life-years (QALYs). It is much the same as cost-effectiveness analysis with the added dimension of a particular point of view – most often that of the patient. According to Jefferson *et al.* (2000:13) when the interventions that are compared produce different outcomes in terms of both quantity and quality of life, they are expressed in utilities. Cost-utility analysis can compare cost, quality, and the quantity of patient years (Bungay & Sanchez, 2003:33). Quite often the results of a cost-utility analysis (Franic *et al.*, 2003:154) are expressed in quality-adjusted-life-year (QALY) gained, or changes in Quality of life (QOL) measurement for a given intervention cost. The QALY, according to Walley *et al.* (2004:191), is a general measure of health outcome that captures changes in mortality and morbidity, and quality of life.

Quality of life is an evaluation of all aspects of our lives, such as where we live, how we live, how we play, and how we work (Bungay & Sanchez, 2003:40). Health-related quality of life is a specific area of investigation within the field of health services and quality of life research. According to Strom and Kimmel (2006:478), quality of life is the description of aspects or areas of physical, social and emotional health that are relevant and important to the patient. Quality

of life measures efficacy in clinical trials and is growing as a valid indicator of whether a medical treatment is beneficial or not (Spilker, 1996:1). Quality of life can be viewed in terms of an individual, group or large population of patients (Perfetto *et al.*, 2003:301). Quality of life can be used to measure the burden of a particular disease and to compare the effect of different diseases on functioning and well-being (Spilker, 1996:2). Some of the key areas of quality of life are as follows:

- Physical status and functioning abilities
- Psychological status and well-being
- Social interactions
- Economic status and factors
- Religious and/or spiritual status

(Perfetto *et al.*, 2003:301).

2.2.4.5.5 Cost-of-illness evaluations

Cost-of-illness is referred to by Bungay and Sanchez (2003:32) as an examination of the overall (direct and indirect) costs of a particular disease to a defined population. The direct and indirect costs of an illness can be used to determine the value of a treatment or prevention strategy. According to Jefferson *et al.*, (2000:18), the methods employed in COI (cost-of-illness) studies include recognition, identification, listing, measurement and valuation of cost generated by an illness. Cost-of-illness measures the economic burden of disease and illness on society (Cox, 2003:91).

Van Jaarsveld *et al.* (1998:837) conducted a cost-of illness study on 424 rheumatoid arthritis patients, to determine the direct cost of RA during the first six years. They concluded that the mean annual direct cost of RA during the first six years of disease was estimated to be £3680 per patient. A few patients generated relatively high costs while 75 % generated lower costs (Van Jaarsveld *et al.*, 1998:845). Another cost-of-illness study done on patients suffering from juvenile idiopathic arthritis (JIA) showed the mean total cost of late JIA was estimated to be €3500 per patient per year, of which direct costs contributed more than half (Minden *et al.*, 2004:836).

Cost-of-illness studies examine the following costs:

- Direct costs – these costs are the responsibility of the health care system, community and family in directly addressing the problem (Jefferson *et al.*, 2000:18).
  - Direct medical costs – the costs incurred in providing medical care (Strom & Kimmel, 2006:474). These costs include hospitalisations, drugs, medical supplies and equipment (Bungay & Sanchez, 2003:28).
  - Direct non-medical costs – the costs incurred because of an illness or the need to seek medical care, for example the cost of transportation (Strom & Kimmel, 2006:474).
- Indirect costs – these costs do not stem directly from transactions for goods or services (Strom & Kimmel, 2006:476), but instead are mostly productivity losses caused by the problem or disease (Jefferson *et al.*, 2000:18). These costs place a burden on the individual, family, society, or the employer, for example morbidity costs incurred from missing work and lost productivity, and mortality costs due to premature death (Bungay & Sanchez, 2003:28).
- Intangible costs – these are usually the costs of pain, grief, suffering and loss of leisure time. The cost of a life is usually included in case of death (Jefferson *et al.*, 2000:18).

2.2.4.6 Summary of some pharmacoeconomic techniques (Bonk, 1999:10)

Technique	**Distinguishing features**
Cost-benefit	Measures the cost of treating an illness, along with monetary equivalents for the treatment's outcomes.
Cost-effectiveness	Measures the costs of treating an illness, but uses clinical measurement's for the treatments outcomes.
Cost-minimisation	Directly compares the costs of treatment options for an illness, assuming equivalence of their outcomes.
Cost-utility	Measures the costs of treating an illness, but uses preference equivalents for the treatment's outcomes.
Cost-of-illness	Identifies and measures the costs of illness itself, but not treatment outcomes.

2.2.5 PHARMACOEPIDEMIOLOGY

2.2.5.1 Historical perspective

Although the development of epidemiology has spanned many centuries, the field only emerged as an area of medical enquiry in the late 19th century. Main events in the advance of epidemiology include James Lind's study on scurvy (1747 – 1753); the standardised registration of births and deaths (early 1800s); and John Snow's observations of a cholera epidemic in London (1849) (Waning & Montagne, 2001:2).

According to Fautrel (2004:175), pharmacoepidemiological studies became obvious in the 1960s when the introduction of the hypnotic agent Thalidomide produced an epidemic of severe birth defects. Other side-effects detected by pharmacoepidemiological studies include thromboembolism associated with combination oral contraceptives and pulmonary fibrosis induced by appetite suppressants. The history of drug regulation, according to Strom (2006:3), parallels the history of major adverse drug reaction "disasters". Each change in pharmaceutical law was directly related to, and a political reaction to, an epidemic of adverse drug reactions. Recent data suggest that approximately 100 000 Americans die each year from adverse drug reactions (ADRs), and 1.5 million US hospitalisations each are caused by ADRs, even though 20 to 70 % of ADRs may be preventable.

2.2.5.2 Definition of pharmacoepidemiology

According to Bergman (2001:31) epidemiology was defined as the study of the distribution of health-related states and procedures in populations, and the application of this study to manage health problems. Drug utilisation studies utilise a variety of information sources that focus on drugs, e.g. wholesale and prescription registers, whereas the term epidemiology implies that pharmacoepidemiological studies are population based, and link health events to drug exposure. According to Strom (2006:3), pharmacoepidemiology can be defined as the study of the use and effects of drugs in large numbers of people.

During the past decades there have been increasing concerns about drug safety (Bergman, 2001:31) that led to the increased importance and use of drug surveillance. According to Fautrel (2004:175), pharmacoepidemiological studies have the ability to find associations between a drug (or drug class) and one or more clinical events that had been missed under the strictly controlled conditions of therapeutic trials. Bergman (2001:31) also states that with the rapidly

growing use of epidemiologic techniques came the recognition of pharmacoepidemiology as a new discipline.

2.2.5.3 Pharmacoepidemiologic study designs and methods

- Case reports - these are reports of events observed in single patients and not in groups (Strom, 2006:18). This report describes a single patient who was exposed to a drug and had experienced an adverse outcome. Case reports are helpful in making a hypothesis about the effects of drugs, which can then be thoroughly tested and studied.
- Cross sectional study - this study uses a prevalence survey of health and illness (Waning & Montagne, 2001:5), in a group or population (or a sample of a group or population) at a certain time. The study may be based on retrolective (previously-recorded) or prolective data (Abramson & Abramson, 1999:22).
- Case control study - this is a retrospective analysis comparing subjects, with the condition (cases) to those without it (controls) with respect to possible risk or causative factors (Waning & Montagne, 2001:5), and differences in exposures (Strom, 2006:19). This type of study is very useful when the aim is to study multiple causes of a single disease. The same cases and controls can be used to examine any number of exposures as potential risk factors (Strom, 2006:19).
- Cohort study - this is an incidence study (Waning & Montagne, 2001:5) that follows a population free of health problems over time and examines subsequent development of problems and factors associated with them. The people are respectively exposed (Strom, 2006:19) and not-exposed to the factor(s), or have different degrees of exposure, and are compared with the resulting development of the disease or study outcome. The people who are followed up are referred to as the cohort (Abramson & Abramson, 1999:22).
- Clinical trials - this is an experimental approach that tests the value of a new treatment or intervention compared with a standard treatment or a placebo. The investigator controls the therapy that each participant receives (Strom, 2006:21).

Drug and prescription use has always been important, and since the 1990s, prescription use has increased considerably. This increase is accompanied by problems associated with the use of certain drugs (e.g., adverse reactions and side-effects). Efficient drugs are always needed and replacing older drugs with newer ones is a key aspect of health care advances. Newer and more specific-acting drugs unfortunately also have problems related with their use (Waning & Montagne, 2001:4) for example:

- Merck & Co. announced a voluntary withdrawal of Vioxx® (rofecoxib) on 30 September 2004. The company's decision, which was effective immediately, was based on new, three-year data from a prospective, randomised, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on Vioxx®) trial (Merck, 2004).

2.2.6 DRUG UTILISATION REVIEW (DUR)

2.2.6.1 Definition of DUR

The World Health Organization (WHO) defines drug utilisation as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences (Waning & Montagne, 2001:162).

2.2.6.2 Introduction

According to Gray and Clarke (1995:281), drug utilisation studies have the provision of principles for decision-making in the drug and health chain in mind, and should give special attention to the resulting medical, social and economic consequences. The process of drug use evaluation (DUE) goes by many names and is also referred to as drug utilisation review (DUR) according to Weber (1999:2). For the purpose of this study the term DUR will be used, rather than DUE.

DUR is a method of improving the quality of patient care (Weber, 1999:2) by enhancing therapeutic outcomes, reducing inappropriate pharmaceutical expenditures and intervening when inappropriate drug use is detected (Strom & Kimmel, 2006:474). The Academy of Managed Care Pharmacy (AMCP) recognise the value of drug use evaluation and its aim to reduce overall health care costs (Weber, 1999:2). According to Waning and Montagne (2001:162) pharmacists conduct drug utilisation studies, as part of their routine activities, and state that DURs are usually done to monitor prescribing patterns. Medications monitored through DUR are chosen according to cost, frequency of use and risk of toxicity. Cost and frequency of use are easily obtained, but the risk of toxicity is typically unknown at the time the DUR is designed. Waning and Montagne (2001:162) also state that drugs, recently approved by the FDA and showing serious adverse effects in phase III trials, are normally chosen to be monitored via DURs.

Drugs can be classified according to their chemical structure or their pharmacological action and therapeutic use. In the anatomical therapeutic chemical (ATC) classification system, the drugs

are separated into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties (WHO, 2007b).

Prescribed daily dose (PDD) – the prescribed daily dose is the average daily amount of a drug that is actually prescribed by a specific group of prescribers for a given period (National Health Services, 2008). The prescribed daily dose (PDD) will be analysed during this study as the data available only include prescriptions claimed during the study period.

Blackburn (1993:20) states that drug use review (DUR) programmes have been a part of efforts to improve prescribing practices in both the institutional and ambulatory care settings in different areas of the world. DUR provides the mechanism for developing standards, assessing current therapy, and implementing a specific intervention followed by re-evaluation of drug utilisation. Drug use evaluation according to Weber (1999:2), is an on-going systematic process designed to maintain the correct and efficient use of drugs, and includes a broad evaluation of patients' prescription and medication data before, during and after dispensing to assure appropriate therapeutic decision making and positive patient outcomes.

Quantitative DUR – the objective of such a study, according to Lee *et al.* (2006:400), is to quantify the present state and developmental trends of drug usage at different levels of the health care system, whether national, regional, local, or institutional. Regularly compiled drug utilisation data or statistics that result from these studies can be used to calculate drug utilisation in populations by age, gender, social class and morbidity to identify areas of potential over- or under-utilisation.

Qualitative DUR – the objective of such a study, according to Lee *et al.* (2006:400), is to measure the appropriateness of drug utilisation, usually by linking prescription data to the reasons for the drug prescribing. Explicit predetermined criteria (such as indications for use, daily dose, length of therapy, etc.) are created to which aspects of the quality, medical necessity, and appropriateness of drug prescribing may be compared.

2.2.6.3 Classification of drug use evaluation categories

- **Prospective DUR** - As the name indicates, prospective DUR occurs before any medication is dispensed (Lee *et al.*, 2006:408). The pharmacist is required to screen for possible drug therapy problems including incorrect dosing, over/under-utilisation, drug-drug interactions, drug-disease interactions, duplicate therapy, and possible abuse (Weber, 1999:2).

  Issues addressed by prospective DUR:

  - Drug-disease contraindications
  - Therapeutic interchange
  - Generic substitution
  - Incorrect drug dosage
  - Inappropriate duration of drug treatment
  - Drug-allergy interactions
  - Clinical abuse/misuse

  (Weber, 1999:2-3)

- **Concurrent DUR** – This review is performed during the treatment and involves continuing monitoring of drug therapy to ensure positive patient outcomes. Pharmacists have the opportunity to alert prescribers to potential problems and to intervene in areas such as drug-drug interactions, duplicate therapy, over- or under-utilisation, and excessive or insufficient dosing (Weber, 1999:3).

  Issues addressed by concurrent DUR:

  - Drug-drug interactions
  - Excessive doses
  - High or low dosages
  - Duplicate therapy
  - Drug-disease interactions
  - Over- and under-utilisation
  - Drug-age precautions
  - Drug-gender precautions

- Drug-pregnancy precautions

(Weber, 1999:3)

- **Retrospective DUR** - This evaluation occurs after the prescription has been dispensed and the patient has received his/her medication (Lee *et al.*, 2006:408), and targets the patterns involving administration of drugs, prescribers and pharmacists. A retrospective review (Weber, 1999:3) may detect and prevent inappropriate use and abuse of drugs and serves as a means for developing prospective standards and target interventions.

  Issues addressed by retrospective DUR:

  - Therapeutic appropriateness
  - Over- and under-utilisation
  - Appropriate generic use
  - Therapeutic duplication
  - Drug-disease contraindications
  - Drug-drug interactions
  - Incorrect drug dosage
  - Inappropriate duration of treatment
  - Clinical abuse/misuse

  (Weber, 1999:3)

According to Skibinski (2004:5.1), drug utilisation review (DUR) is a process used to assess the appropriateness of drug therapy by engaging in the assessment of data on drug use, and actual behaviour (Lee *et al.*, 2006:408) in a specific health care environment against predetermined criteria and standards. A commonly used criterion, for example, is that patients should not receive more than one non-steroidal anti-inflammatory drug at one time. Lee *et al.* (2006:408) also state that the relevant criteria have been developed to identify some of the following problems: drug-drug interaction, drug-disease interactions, drug-age interactions, drug allergy interaction, over- or under-dosing, duplication of therapeutic class, etc.

2.2.6.4 Steps in conducting a drug use review

According to Weber (1999:4) the following steps can be followed when conducting a drug use review:

- Identify or determine optimal use – criteria are defined to allow for comparisons of optimal use with actual use.
- Measure actual use – this step is where data are gathered to measure the actual use of medications.
- Compare – this involves the comparison between optimal or appropriate and actual use.
- Intervene – this is the step where corrective action is implemented.
- Evaluation of programme – the last step is to evaluate the effectiveness of the DUR programme (Weber, 1999:4).

2.2.6.5 Medication use evaluation

Medication use evaluation is a prospective evaluation that focuses on the outcome of the patient's medication therapy according to predetermined criteria. The objective of the evaluation is to optimise and improve medication management and to better the patient's quality of life throughout all phases of the medication use process (Skibinski, 2004:5.1).

2.2.7 DISEASE MANAGEMENT

Disease management, according to Faxon *et al.* (2004:2653), addressed the full spectrum of health care and aims to be an integrated system for managing patient health care (improve health rather than simply treat disease). The main indicator of success in disease management should be patient outcomes and quality of care, and not simply the ability to reduce health care expenditures. The NHS (national health services) see DM (disease management) as a way to offer services that can be bound tight to clinical protocols, excercising an impact on costs and reshaping services in specific disease areas (Lilley, 1998:1).

Disease management, however, is never a finished product, and Couch (1997:4) defines it as "*a knowledge-based process intended to improve continuously the value of health care delivery from the perspectives of those who receive, purchase, provide, supply and evaluate it*".

According to McDonald *et al.* (2004:72) disease management should be a system of care, with the focus on the patient. Compartmentalisation of care should be avoided to give preventative medicine rather that reactive medicine and poor patient care.

Disease management, according to McDonald *et al.* (2004:75), aims to accomplish the following:

- Contain costs
- Improve health outcomes
- Reduce variations in care
- Improve the quality of care provided
- Maintain or increase drug sales

The application of pharmacoeconomics in a disease management context provides decision makers with a much richer picture from which to make choices (McDonald *et al.*, 2004:76).

2.2.8 CHAPTER SUMMARY

This chapter has shown that NSAIDs have a great deal of side-effects, some of which are life-threatening. However, these drugs are not only used in the treatment of various pains and aches, but are also essential in the treatment of conditions such as Rheumatoid- and Osteoarthritis. Some of the issues discussed in this chapter, as well as the prevalence and costs associated with Coxibs, will be investigated in Chapter 5. This chapter also discussed the principles of pharmacoeconomics, drug-utilisation review and managed health care. The empirical investigation will be discussed in chapter 4.

CHAPTER 3: EMPIRICAL INVESTIGATION

3.1 INTRODUCTION

In this chapter the aims and objectives, research methodology, data source and medicine claim databases will be discussed.

3.2 AIMS AND OBJECTIVES

3.2.1 General research objective

The general research objective of this study was to review certain usage and cost patterns of non-steroidal anti-inflammatory drugs in a section of the private health care sector for the period 2004 to 2006 by using two different medicine claims databases.

3.2.2 Specific research objectives

The research objectives consisted of two phases, namely a literature review, and an empirical investigation. The research objectives of the two phases included the following:

3.2.2.1 Literature review

The specific objectives of the literature study included the following:

- To conceptualise the usage and side-effects of NSAID use.
- To review specific cyclo-oxygenase-2 inhibitor (Coxib) use and aspects of the product's withdrawal from the market.
- To conceptualise from the literature what managed health care, drug utilisation, pharmacoeconomics and disease management entail.

3.2.2.2 Empirical investigation

The specific objectives of the empirical study for both medicine claim databases were:

- To investigate the usage patterns of NSAID therapy over the study period.
- To analyse and calculate the cost of NSAID therapy over the study period.
- To review the use of Coxibs before and after the discontinuing of Vioxx® (refer to paragraphs 2.1.6.3 and 2.1.6.4) on Medicine claim database I.

- To investigate the usage patterns of Coxib therapy.
- To analyse and calculate the cost of Coxib therapy.
- To investigate the usage patterns of NSAID therapy per sub-pharmacological group (according to MIMS® classification) over the study period.
- To analyse and calculate the cost of NSAID therapy per sub-pharmacological group (according to MIMS® classification) over the study period.
- To identify the top twenty NSAIDs according to prevalence, cost and gender for Medicine claim database M.
- To identify and analyse the number of NSAID containing prescriptions per patient for Medicine claim database M.
- To identify the prevalence of NSAID use according to active ingredient for Medicine claim database M.
- To investigate the prevalence and cost of NSAID medicine items according to age for Medicine claim database M.

3.3 RESEARCH DESIGN

This study can be classified as a retrospective, quantitative research where drug therapy is reviewed after the patient has received the medication. A retrospective drug review may detect patterns in prescribing, dispensing, or administering of drugs to prevent recurrence of inappropriate use (Weber, 1999:3).

3.4 RESEARCH METHODOLOGY

3.4.1 Data source

The data used in this study were obtained from two pharmacy benefit management companies. All prescriptions claimed during the study period, containing one or more medicine items were included under general prescriptions and all prescriptions containing one or more NSAID medicine item classified as NSAID prescriptions. The data used in this study were investigated under the following categories:

- Prevalence
- Cost
- Age
- Gender

For the purpose of this study the data from medicine claim database M were divided into five age groups, which are as follows:

Age group 1	$0 \leq 9$ years
Age group 2	$9 \leq 19$ years
Age group 3	$19 \leq 45$ years
Age group 4	$45 \leq 59$ years
Age group 5	$59 <$ years

Data were extracted from Medicine claim database I for the period 2004 to 2006, and from Medicine claim database M for the period 2005-2006. The difference in study periods was due to the availability of data from the two different medicine claim databases. For security, ethical, and patient and provider identification reasons, the two medicine claim databases are not identified by name.

3.5 DATA ANALYSIS

3.5.1 Data application and analysis

This step consisted of two parts. Firstly the data categories were retrospectively viewed and any deviations were marked either for further review or as potential targets for intervention. Secondly the data were analysed by means of the SAS 9.1® programme (SAS for Windows, 9.1, 2005).

3.5.2 Statistical analysis

The following statistical methods were used to analyse the data.

3.5.2.1 Average value (arithmetic mean)

The arithmetic mean of a set of (n) measurements is equal to the sum of the measurements divided by (n) (Mendenhall *et al.*, 1993:38). The arithmetic mean or average is the value each item in the distribution would have if all the values were shared equally among all the items (Harper, 1991:117).

$$\text{Mean} = \bar{x} = \frac{\sum x}{n}$$

Where: x = any value in the data set

$\sum x$ = the sum of all the given x values

n = the number of the measurements in the sample or data set

3.5.2.2 Standard deviation

The standard deviation of a set of measurements (n), is equal to the positive square root of the variance (Mendenhall *et al.*, 1993:51). The standard deviation is the most frequent measure of variability, and is a kind of average of the distances of the observed values from the mean. If many of the observations are far above or below the mean, the standard deviation is large (Anderson & Finn, 1996:113).

$$\text{Standard deviation} = s = \sqrt{s^2} = \sqrt{\frac{\sum_{n-1}^{n}(x_i-\bar{x})^2}{n-1}}$$

Where : s = standard deviation

n = the number of observations

$\bar{x}$ = the mean

x_i = any value in the data set

3.5.2.3 Cost prevalence index (CPI)

The cost prevalence index can be used to indicate and monitor changes in drug usage. The following equation is used for the calculation of the cost index (Serfontein, 1989:180).

$$\text{Cost index} = \frac{\text{Cost (\%)}}{\text{Prevalence (\%)}}$$

In context of the study the cost index can be interpreted as follows (Serfontein, 1989:180):

If cost index < 1 then the therapy utilised is relatively inexpensive

If cost index = 1 then there is equilibrium between the costs and prevalence of the therapy

If cost index > 1 then the therapy utilised is relatively expensive

3.5.2.4 Effect sizes (d-values)

Effect size according to Anderson and Finn (1996:620) is the number of standard deviations that separate the group means. Effect size can be calculated as follows:

$$\text{Effect size} = d = \frac{\bar{x}_a - \bar{x}_b}{s_{\max}}$$

Where : $\bar{x}_a$ = the average medicine cost of population a

$\bar{x}_b$ = the average medicine cost of population b

$s_{\max}$ = the maximum standard deviation between a and b

The d-values can be interpreted as follows (Steyn, 1999:3):

[d] = 0.2 (small effect with no practical significant difference).

[d] = 0.5 (medium effect which is observable and may be significant).

[d] = 0.8 (large effect which is significant and of practical importance).

[d] > 0.8 (assumed to have practical significant value).

3.6 MEASURING CRITERIA CATEGORIES FOR THE DATA ANALYSIS

The following criteria were selected to achieve the objectives set out in this study:

- Medicine items
- Prevalence
- Cost

3.6.1 Medicine items

Medicine items was analysed to evaluate the total number of medicine items per prescription, average number of medicine items per prescription, total cost of all medicine items, and average cost of medicine items for all NSAIDs as well as for all medicine items in the medicine claim database.

3.6.2 Prevalence

In this study the prevalence of the medicine items was analysed as follows:

- The prevalence of all medicine items of the total medicine claim database claimed during the study period.
- The prevalence of all NSAID medicine items claimed during the study period.
- The prevalence of all Coxibs claimed during the study period.
- The prevalence of Coxib items were compared (per term) before and after the withdrawal of Vioxx® from the market (30 September 2004).

3.6.3 Cost

The total medicine cost, the average cost per prescription, the average cost per medicine item, as well as the cost prevalence index for NSAIDs were analysed as follows:

- The medicine costs of all medicine items claimed from Medicine claim database M for the period 1 January 2005 to 31 December 2006, were compared.
- The costs of all medicine items claimed from Medicine claim database I for the period 1 January 2004 to 31 December 2006, were compared.
- The medicine costs of all NSAID medicine items claimed from Medicine claim database M for the period 1 January 2005 to 31 December 2006, were compared for different time periods.

- The medicine costs of all NSAID medicine items claimed from Medicine claim database I for the period 1 January 2004 to 31 December 2006, were compared for different time periods.
- The medicine costs of all NSAID items claimed per year (1 January 2004 to 31 December 2006) for Medicine claim database M and Medicine claim database I were compared.
- The medicine costs of all Coxib items claimed per year during the study period for both Medicine claim database M and Medicine claim database I were compared.
- The medicine cost of Coxib items was compared (per term) before and after the withdrawal of Vioxx® from the market (30 September 2004).

3.7 RELIABILITY AND VALIDITY

Both Medicine claim database I and Medicine claim database M were used to obtain data for the study. Data were obtained directly from the medicine claim database which made direct manipulation of the data by the researcher impossible. The personal information of patients, prescribers and medical schemes was not disclosed due to ethical reasons. The two pharmacy benefit management companies (PBMs) gave permission for the data to be used in this study, and the ethical committee of the North-West University approved the study (NWU-0046-08-S5).

3.8 RESULTS AND DISCUSSION

The results of the empirical investigation have been discussed in Chapter 4.

3.9 CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations based on the results of the empirical investigation have been discussed in Chapter 5.

3.10 CHAPTER SUMMARY

In this chapter the general and specific research objectives, data source, data analysis and statistical analysis were discussed. The analysis as well as the results of the empirical study is reported in Chapter 4.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter the results of the empirical investigation will be discussed. The cost and prescribing patterns of non-steroidal anti-inflammatory (NSAID) medicine items were investigated by means of data from medicine claim database I for the study periods 1 January 2004 to 31 December 2004, 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006. During this study special attention was given to the usage and cost of Coxib (specific cyclo-oxygenase-2 inhibitor) medicine items after the discontinuation of Vioxx®. The cost and prescribing patterns of non-steroidal anti-inflammatory (NSAID) medicine items were also investigated by means of data from medicine claim database M for the study periods 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006. The difference in time periods for the two medicine claim databases are due to the availability of electronic data.

The data analysed in this study have been classified according to the MIMS® classification system (Appendix A.1) (Snyman, 2007:11a). Analyses on all NSAIDs, (pharmacological group 4.1 according to the MIMS® classification system) were done as well as analyses on three sub-pharmacological groups namely COX-inhibitors (sub-pharmacological group 4.1.1 according to the MIMS® classification system), Selective COX-2 inhibitors (sub-pharmacological group 4.1.2 according to the MIMS® classification system) and specific cyclo-oxygenase-2 inhibitors (Coxibs) (sub-pharmacological group 4.1.3 according to the MIMS® classification system).

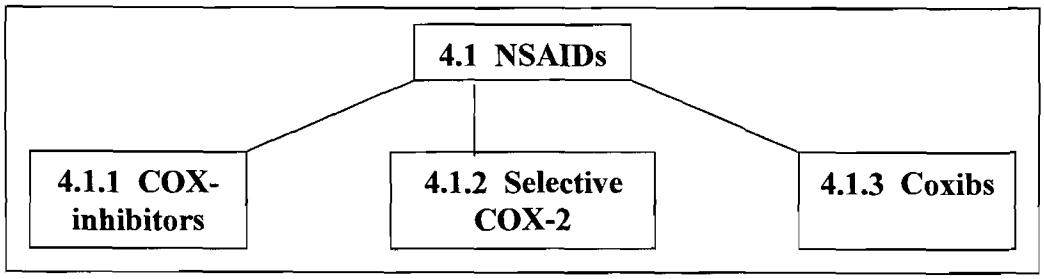

Figure 4.1 Pharmacological and sub-pharmacological classification according to the MIMS classification system (Snyman, 2007:82).

The outline for this study is shown in the diagrammes in Figure 4.2, Figure 4.3, and Figure 4.4, and present the analysis pathways used for both medicine claim databases.

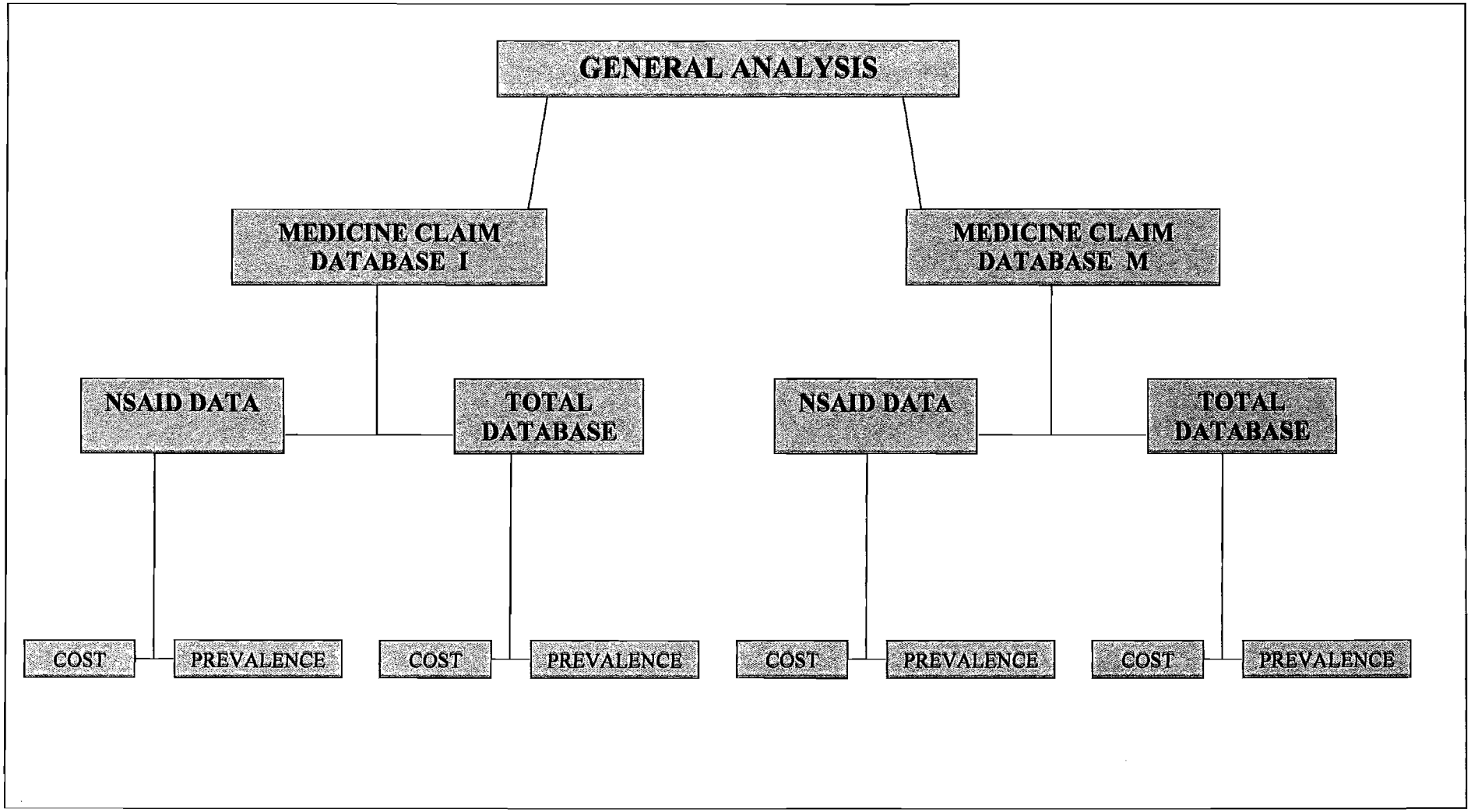

Figure 4.2 Schematic presentation of the general study analysis

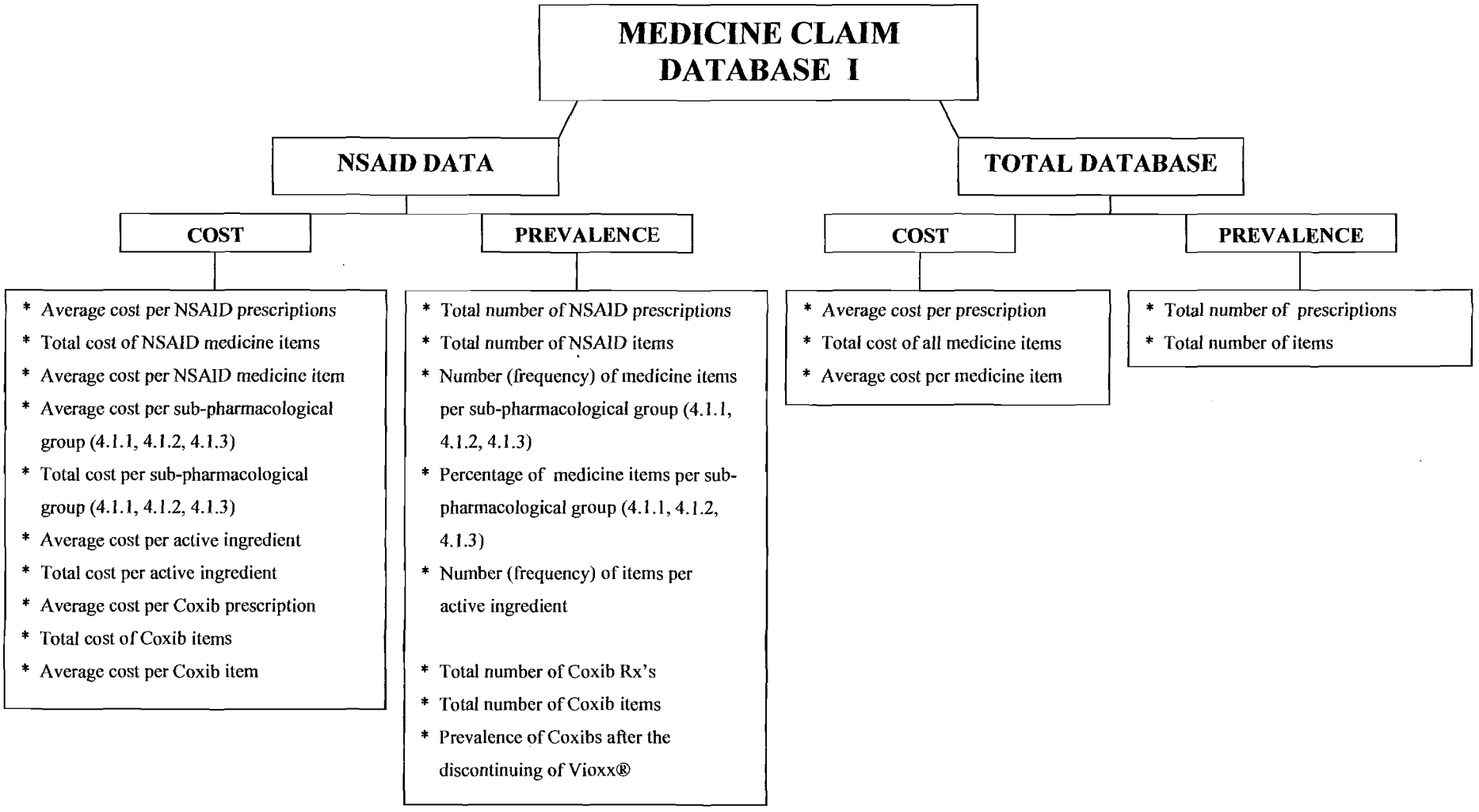

Figure 4.3 Schematic presentation of analysis for Medicine claim database I

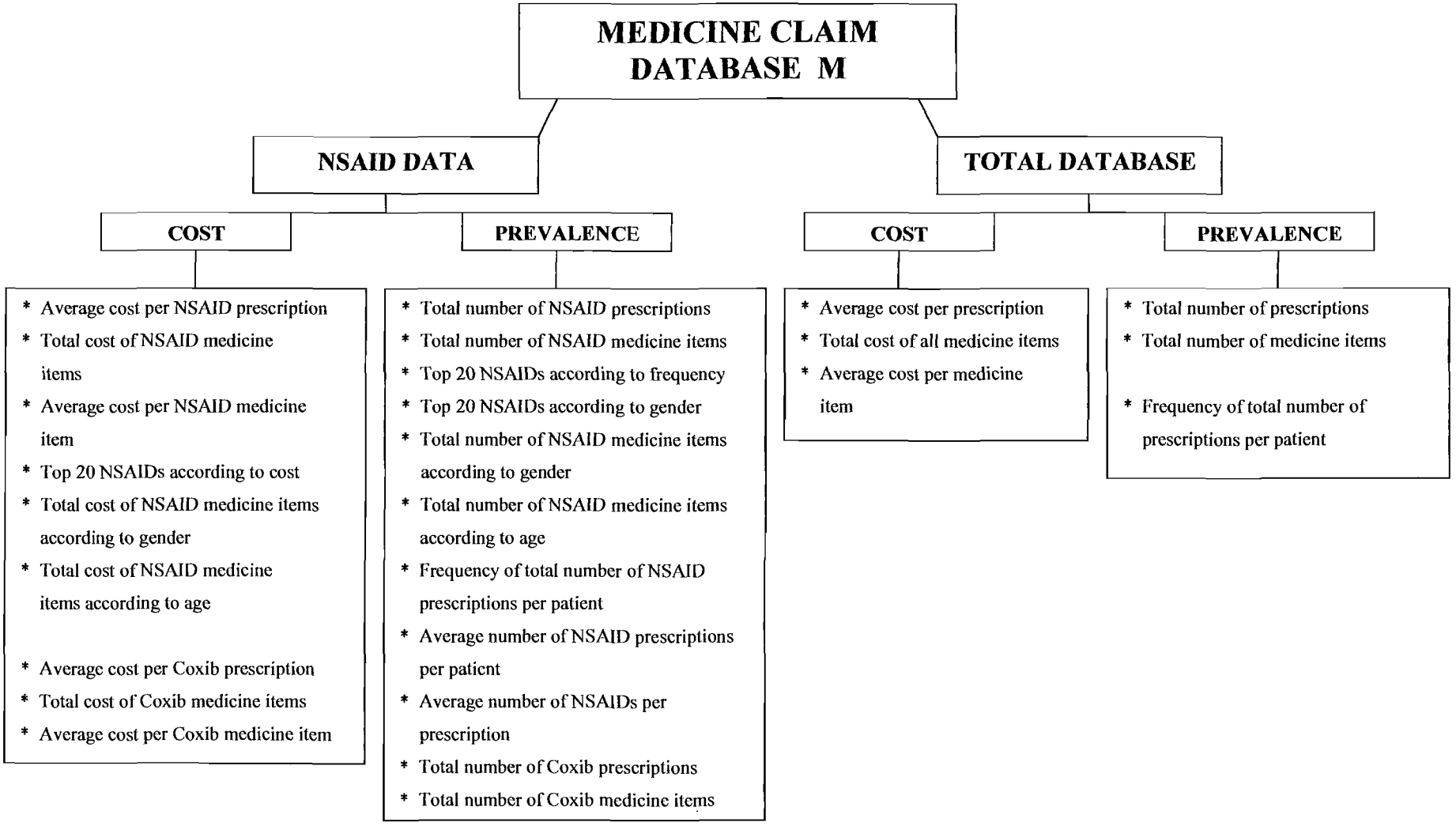

Figure 4.4 Schematic presentation of the analysis for Medicine claim database M

4.2 DISCUSSION OF THE RESULTS FOR MEDICINE CLAIM DATABASE I

4.2.1 Notes related to the interpretation of the results

For the purpose of this study, each year will consist of three time periods. In total there will be 9 time periods. The first study year consists of Term 1, Term 2 and Term 3. Equally the second study year consists of Term 4, Term 5 and Term 6, and the third study year of Term 7, Term 8 and Term 9. These time period categories will be applied to both medicine claim databases.

The time periods will be as follows:

Term 1	1 January 2004 to 30 April 2004
Term 2	1 May 2004 to 31 August 2004
Term 3	1 September 2004 to 31 December 2004
Term 4	1 January 2005 to 30 April 2005
Term 5	1 May 2005 to 31 August 2005
Term 6	1 September 2005 to 31 December 2005
Term 7	1 January 2006 to 30 April 2006
Term 8	1 May 2006 to 31 August 2006
Term 9	1 September 2006 to 31 December 2006

- For the purpose of this study sub-pharmacological group 4.1.1 will be referred to as COX-inhibitors, sub-pharmacological group 4.1.2 will be referred to as Selective COX-2 inhibitors, and sub-pharmacological group 4.1.3 as Coxibs, according to the MIMS classification (Snyman, 2007:82).
- Some of the tables will not add up to one hundred per cent because percentages were rounded off to two decimals or the nearest rand.
- The effect sizes (d-values) were calculated and described in the text, but not indicated in any tables.
- The results of the two medicine claim databases were presented separately.
- For the purpose of this study, an anti-inflammatory drug (NSAID) prescription, is any prescription that contains one or more NSAID items.
- For the purpose of this study, a general prescription, is any prescription that contains one or more medicine items.
- Due to the nature and extent of the study, with reference to the general and specific objectives (refer to paragraph 1.3) to investigate the related usage and cost patterns of the

active ingredients of NSAIDs, the effect of possible substitution of generic equivalents was not investigated. This may have an influence on cost-related aspects and may be regarded as a limitation of the study.

- The standard deviations for average costs were indicated in the relevant tables but not shown in any figures. The standard deviations for the averages in figure 4.5 and figure 4.7 were indicated in table 4.1, while the standard deviations for the averages in figure 4.11 were indicated in table 4.3.
- Due to technical reasons the size and font of the text and tables may differ.

4.2.2 General analysis for Medicine claim database I for the years 2004, 2005 and 2006

4.2.2.1 The cost and prevalence of NSAID medicine items

Table 4.1 shows the prescribing patterns of all the medicine items in medicine claim database I, as well as all the NSAID medicine items, for the three study years (1 January 2004 to 31 December 2004, 1 January 2005 to 31 December 2005, and 1 January 2006 to 31 December 2006).

With reference to table 4.1, it can be determined that 8.99 % (n = 233 336) of the total number of 2 595 242 prescriptions dispensed according to medicine claim database I for the period 1 January 2004 to 31 December 2004, were non-steroidal anti-inflammatory drug (NSAID) prescriptions. The percentage of NSAIDs increased for the following year (period 1 January 2005 to 31 December 2005) to 9.30 % (n = 150 840), and increased again for the next year (period 1 January 2006 to 31 December 2006) to 10.48 % (n = 104 501). Thus, over a three-year period the percentage of NSAID prescriptions increased from 8.99 % in 2004 to 10.48 % in 2006 while the total number of general prescriptions decreased over the same period from 2 595 242 prescriptions in 2004 to 996 787 in 2006. Joubert (2002:260) found that NSAID prescriptions accounted for 10 % of all prescriptions claimed for a year (1 July 1999 to 30 June 2000). Although the total number of prescriptions, according to table 4.1, decreased from 2004 to 2006, the average number of medicine items per prescription amounted to an average of 2.04 (±1.27) medicine items per prescription in 2004, an average of 2.22 (±1.37) medicine items per prescription in 2005 (d-value of 0.13), and an average of 2.38 (±1.44) medicine items per prescription in 2006 with a d-value of 0.11 from 2005 to 2006. The average number of NSAID medicine items per prescription showed no significant change with 1.03 (±0.17) NSAID medicine items per prescription in 2004, 1.05 (±0.22) NSAID medicine items per prescription in 2005 (d-value 0.09) and 1.08 (±0.27) NSAID medicine items per prescription in 2006 with a d-value of 0.11 from 2005 to 2006.

Table 4.1 Cost and prevalence of all medicine items for Medicine claim database I (2004 – 2006)

COST AND PREVALENCE OF ALL MEDICINE ITEMS DURING 2004 TO 2006 FOR MEDICINE CLAIM DATABASE I																
		Total data						NSAID data								
Year	Term	Total number of Rx	Average number of medicine items / Rx	Average cost / Rx (R)	Total number medicine items	Average cost per medicine item (R)	Total cost of all medicine items (R)	Total number NSAID Rx's	Percent-age of NSAID Rx's (%) *	Average number NSAIDs /Rx	Average cost /NSAID Rx (R)	Total number of NSAID medicine items	Percent-age of NSAID medicine items (%)*	Average cost /NSAID medicine item (R)	Total cost of NSAID medicine items (R)	Percent-age of total cost of NSAID medicine items (%)
2004	1	713470	1.91 (±1.2)	278.82 (±476.38)	1363571	145.89 (±283.72)	198933607.00	62492	8.76	1.03 (±0.16)	140.02 (±127.98)	64132	4.70	136.44 (±126.06)	8750301.85	4.40
	2	935640	2.09 (±1.2)	259.42 (±370.98)	1953833	124.23 (±208.03)	242720711.00	84702	9.05	1.03 (±0.17)	115.70 (±114.85)	87225	4.46	112.36 (±112.16)	9800485.42	4.04
	3	946132	2.10 (±1.3)	232.07 (±354.89)	1988442	110.42 (±202.84)	219566683.00	86142	9.10	1.03 (±0.17)	85.81 (±89.13)	88581	4.45	83.45 (±87.23)	7392199.55	3.37
	Total	2595242	2.04 (±1.27)	254.78 (±397.84)	5305846	124.62 (±228.55)	661221000.00	233336	8.99	1.03 (±0.17)	111.18 (±112.14)	239938	4.52	108.12 (±109.89)	25942986.82	3.92
2005	4	517926	2.17 (±1.34)	245.63 (±376.04)	1124635	113.12 (±209.13)	127217012.00	49261	9.51	1.04 (±0.21)	80.61 (±87.96)	51352	4.57	77.33 (±84.63)	3971139.39	3.12
	5	609044	2.27 (±1.39)	243.70 (±396.39)	1384135	107.23 (±222.57)	148423312.00	56030	9.20	1.05 (±0.22)	74.06 (±82.43)	58648	4.24	70.75 (±79.23)	4149614.75	2.80
	6	494766	2.22 (±1.37)	263.13 (±438.46)	1098222	118.54 (±248.86)	130188773.00	45549	9.21	1.05 (±0.23)	77.47 (±85.28)	47975	4.37	73.55 (±82.11)	3528596.97	2.71
	Total	1621736	2.22 (±1.37)	250.24 (±403.60)	3606992	112.51 (±226.99)	405829097.00	150840	9.30	1.05 (±0.22)	77.23 (±85.17)	157975	4.38	73.74 (±81.94)	11649351.11	2.87
2006	7	329487	2.36 (±1.43)	276.87 (±421.55)	778669	117.16 (±227.74)	91226251.00	33675	10.22	1.07 (±0.26)	75.29 (±95.37)	36048	4.63	70.34 (±90.79)	2535515.34	2.78
	8	348210	2.40 (±1.44)	271.06 (±420.85)	834501	113.10 (±229.16)	94386321.00	35720	10.26	1.08 (±0.27)	72.56 (±91.10)	38460	4.61	67.39 (±86.52)	2591776.79	2.75
	9	319090	2.37 (±1.45)	293.17 (±460.82)	757402	123.51 (±256.44)	93548259.00	35106	11.00	1.08 (±0.28)	83.91 (±100.24)	38033	5.02	77.45 (±94.46)	2945742.61	3.15
	Total	996787	2.38 (±1.44)	280.06 (±434.37)	2370572	117.76 (±237.81)	279160832.00	104501	10.48	1.08 (±0.27)	77.25 (±95.74)	112541	4.75	71.73 (±90.73)	8073034.74	2.89

**Rx refers to prescription

* The number of NSAID preseriptions and number of NSAID items, according to terms and years, were calculated as a percentage of the total number of prescriptions and total number of items in the medicine claim database.

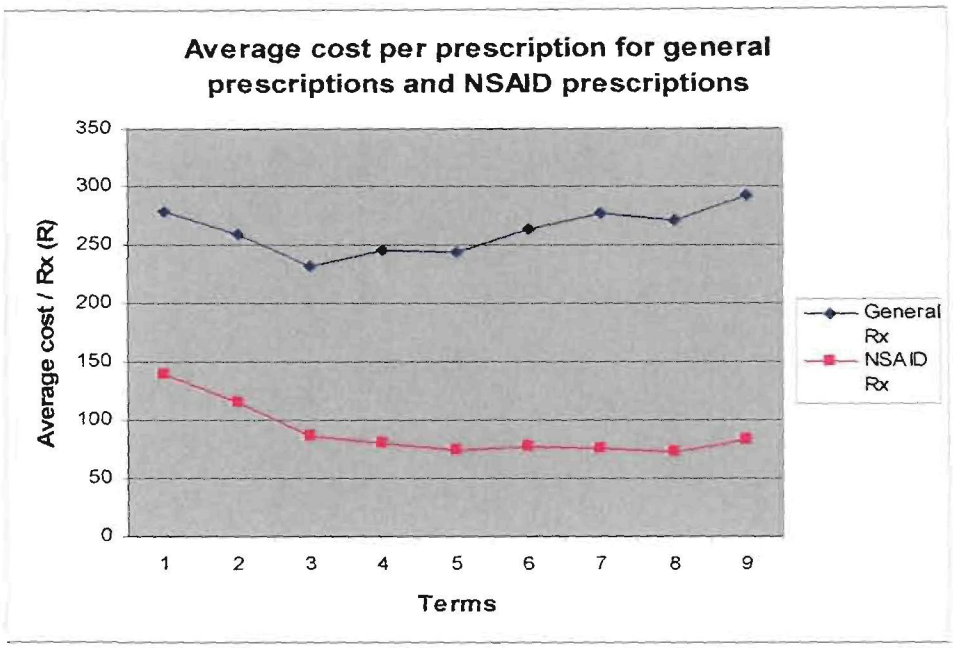

Figure 4.5 The average cost per prescription for Medicine claim database I

The average cost per general prescription according to table 4.1 shows insignificant changes from R254.78 (±397.78) in 2004, to R250.00 (±403.60) for 2005 (d-value 0.01), and R280.06 (±434.37) in 2006 with a d-value 0.06 from 2005 to 2006. The average cost per NSAID prescription decreased from R111.18 (±112.14) in 2004 to R77.23 (±85.17) in 2005 (d-value 0.3) to R77.25 (±95.74) in 2006. The average cost per NSAID prescription for Term 1 through to Term 9 is presented in figure 4.5. The sharp decrease in Term 3 can possibly be ascribed to the withdrawal of Vioxx® from the market in September 2004 (Merck, 2004).

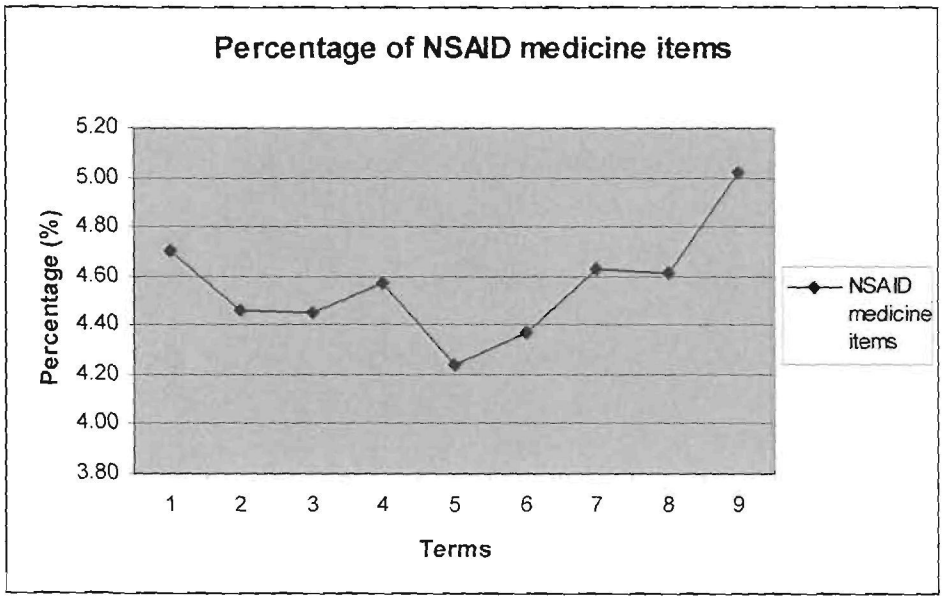

Figure 4.6 The percentage of NSAID medicine items for Medicine claim database I

According to the results in table 4.1 NSAID medicine items represented 4.52 % (n=239 938) of all medicine items (N=5 305 846) during 2004, and decreased to 4.38 % (n=157 975) of all medicine items (N=3 606 992) during 2005, and increased again to 4.75 % (n=112 541) of all medicine items (N=2 370 572) during 2006. Figure 4.6 illustrates the changes in percentage of NSAID medicine items over the three-year period, starting with a 4.70 % (n=64 132) of NSAID medicine items in Term 1 through to 5.02 % (38 033) in Term 9.

Table 4.1 shows that the average cost per medicine item decreased from R124.62 (±228.55) in 2004, to R112.51 (±226.99) in 2005, and slightly increased again to R117.76 (±237.81) in 2006. The average cost per NSAID medicine item showed a similar trend, as it decreased from R108.12 (±109.89) in 2004, to R73.74 (±81.94) in 2005 and decreased again to R71.73 (±90.73) in 2006. These changes in the average cost per medicine item and NSAID medicine item can possibly be related to the introduction of the (R26 / 26 %) regulated dispensing fee model in 2004. Most of the medical schemes implemented this model during the largest part of 2005 and 2006 (Bester, 2007:2). According to Mediscor's medicine review for 2006, the average cost per medicine item for all medicine items decreased approximately 17 % from 2004 to 2005. The figure 4.7 illustrates the decrease of the average cost per NSAID medicine item from Term 1 (R136.44 ±126.06) to Term 9 (R77.45 ±94.46). There was a steady decrease in average cost per NSAID medicine item from Term 1 to Term 8, with a sudden increase in Term 9 to R77.45 (±94.46). This sudden increase in Term 9 can be attributed to Prexige® (lumiracoxib) presenting an average cost of R187.51 (±108.36) for Term 9 (Appendix B, Table B.1.1). It was released on the South African market during April 2006 (South Africa, 2006). The above aspects were not further investigated due to the fact that it is outside the scope of this study.

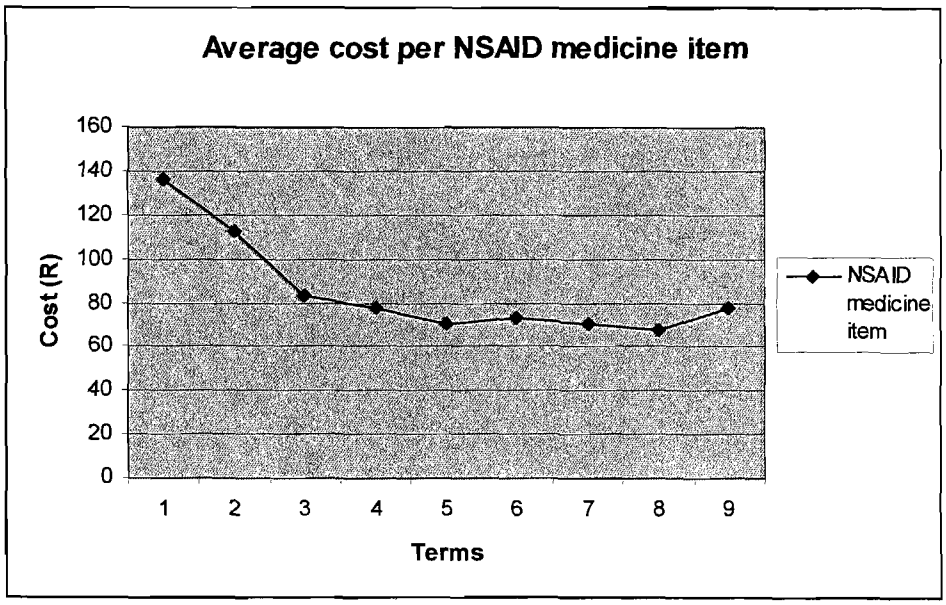

Figure 4.7 The average cost per NSAID medicine item for medicine claim database I

According to table 4.1 the total cost of all NSAID medicine items amounted to R25 942 986.82 (n=239 938) in 2004, decreased to R11 649 351.11 (n=157 975) in 2005, and decreased again to R8 073 034.74 (n=112 541) in 2006. The percentage of the total cost of NSAIDs was determined (table 4.1) and is shown in figure 4.8 below. The cost percentage of NSAID medicine items were 3.92 % in 2004, 2.87 % in 2005, and 2.89 % in 2006. Initially a strong decline in cost is shown with the withdrawal of, first Vioxx® in 2004 and then Bextra® in 2005, from the market.

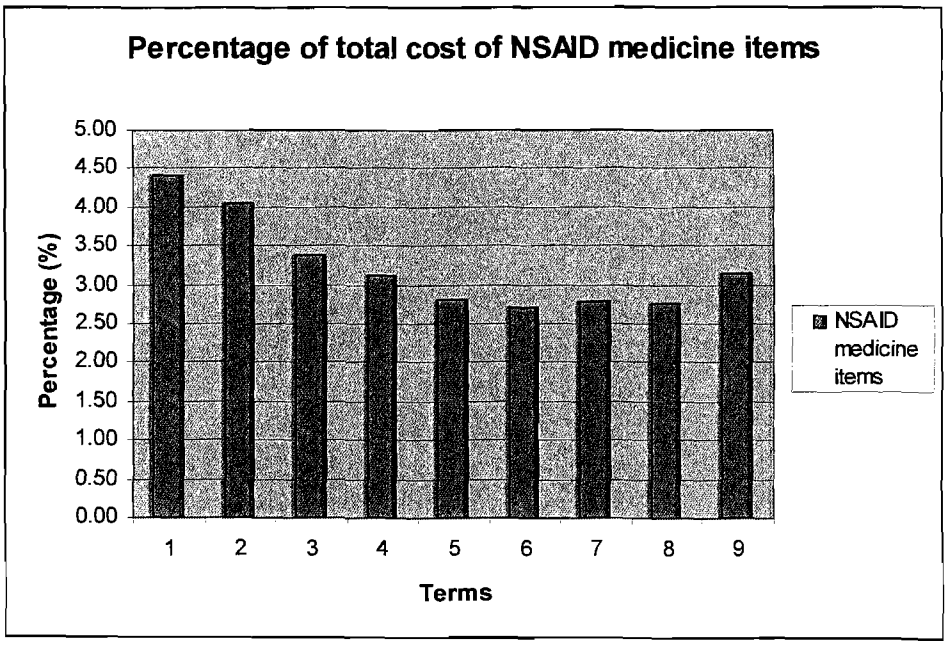

Figure 4.8 The percentage of the total cost of NSAID medicine items for Medicine claim database I

Joubert (2002:261) found that in the year 2000, NSAID medicine items accounted for approximately 4 % of the cost of all medicine items over a year period with a total cost of R 416 919 997.00 while in this study (table 4.1), only six years later, NSAID medicine items represented only approximately 2 % (R8 073 034.74) of the NSAID cost spent in 2000 (R416 919 997.00 0). This change could be due to the number of medical schemes contracted to the medicine claim database I and the changes in the price structure with the introduction of the (R26 / 26 %) regulated dispensing fee model in 2004, as well as the effects of generic substitution that were not investigated in this study.

4.2.2.2 The prevalence of different pharmacological groups for Medicine claim database I

According to table 4.2 COX-inhibitors (sub-pharmacological group 4.1.1) represented 67.2 % (n=161 306) of the total prevalence of all NSAIDs in 2004, and increased to 79.0 % (n=124917) in 2005 and 80.6 % (n=90 702) in 2006. COX-2 inhibitors (sub-pharmacological group 4.1.2)

initially recorded a relatively small change in total prevalence with a decrease from 12.8 % (n=30 694) in 2004 to 12.5 % (n=19 784) in 2005, and a larger decrease to 8.4 % (n=9 484) in 2006.

Table 4.2 The prevalence of different sub-pharmacological groups

PREVALENCE OF THE TOTAL NUMBER OF NSAID ITEMS PER SUB-PHARMACOLOGICAL GROUP FOR MEDICINE CLAIM DATABASE 1 FOR 2004-2006								
Year	**Term**	**Sub-pharmacological group**	**Total number of items (n)**	**Total number of items (%)***	**Average cost (R)**	**Total cost (R)**	**Cost percentage (%)**	**Cost prevalence index****
2004	**1**	4.1.1	41998	65.49	90.79 (±80.76)	3812883.03	43.57	0.67
		4.1.2	7705	12.01	103.19 (±61.43)	795098.16	9.09	0.76
		4.1.3	14429	22.50	287.08 (±142.42)	4142320.66	47.34	2.10
	2	4.1.1	59213	67.89	76.75 (±73.14)	4544528.93	46.37	0.68
		4.1.2	10142	11.63	75.61 (±56.63)	766816.50	7.82	0.67
		4.1.3	17870	20.49	251.21 (±132.70)	4489139.99	45.81	2.24
	3	4.1.1	60095	67.84	61.26 (±61.97)	3681503.15	49.80	0.73
		4.1.2	12847	14.50	54.92 (±37.70)	705585.55	9.55	0.66
		4.1.3	15639	17.66	192.15 (±113.15)	3005110.85	40.65	2.30
	Total	4.1.1	161306	67.23	74.63 (±72.31)	12038915.11	46.41	0.69
		4.1.2	30694	12.79	73.87 (±54.49)	2267500.21	8.74	0.68
		4.1.3	47938	19.98	242.74 (±135.27)	11636571.50	44.85	2.25
2005	**4**	4.1.1	39802	77.51	63.11 (±63.52)	2511890.10	63.25	0.82
		4.1.2	6481	12.62	57.59 (±38.51)	373240.96	9.40	0.74
		4.1.3	5069	9.87	214.24 (±134.70)	1086008.33	27.35	2.77
	5	4.1.1	47305	80.66	57.22 (±58.27)	2706664.17	65.23	0.81
		4.1.2	7210	12.29	62.32 (±39.92)	449338.96	10.83	0.88
		4.1.3	4133	7.05	240.41 (±128.25)	993611.62	23.94	3.40
	6	4.1.1	37810	78.81	55.64 (±53.81)	2103748.51	59.62	0.76
		4.1.2	6091	12.70	65.27 (±39.10)	397574.82	11.27	0.89
		4.1.3	4074	8.49	252.15 (±123.54)	1027273.64	29.11	3.43
	Total	4.1.1	124917	79.07	58.62 (±58.80)	7322302.78	62.86	0.79
		4.1.2	19782	12.52	61.68 (±39.33)	1220154.74	10.47	0.84
		4.1.3	13276	8.40	234.02 (±130.35)	3106893.59	26.67	3.17

Table 4.2 (continued)

Year	Term	Sub-pharmacological group	Total number of items (n)	Total number of items (%)	Average cost (R)	Total cost (R)	Cost percentage (%)	Cost prevalence index
2006	7	4.1.1	30009	83.25	48.66 (±49.96)	1460291.99	57.59	0.69
		4.1.2	3315	9.20	73.73 (±41.61)	244429.44	9.64	1.05
		4.1.3	2724	7.56	304.99 (±138.66)	830793.91	32.77	4.33
	8	4.1.1	31872	82.87	45.63 (±47.81)	1454232.13	56.11	0.68
		4.1.2	3296	8.57	72.74 (±40.92)	239755.03	9.25	1.08
		4.1.3	3292	8.56	272.72 (±129.91)	897789.63	34.64	4.05
	9	4.1.1	28821	75.78	44.70 (±47.41)	1288291.14	43.73	0.58
		4.1.2	2873	7.55	76.50 (±43.73)	249784.28	8.48	1.12
		4.1.3	6339	16.67	226.80 (±123.57)	1437667.19	48.80	2.93
	Total	4.1.1	90702	80.59	46.34 (±48.44)	4202815.26	52.06	0.65
		4.1.2	9484	8.43	74.23 (±42.05)	703968.75	8.72	1.03
		4.1.3	12355	10.98	256.27 (±132.70)	3166250.73	39.22	3.57

* The number of NSAID items per sub-pharmacological group, were calculated as a percentage of the total number of items in the medicine claim database, in terms as well as years.

** Refer to paragraph 3.5.2.3

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)
4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)
4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

However, the prevalence of Coxibs (sub-pharmacological group 4.1.3) decreased significantly from 19.9 % (n=47 938) in 2004 to 8.4 % (n=13 276) in 2005, and increased slightly to 10.9 % (n=12 355) in 2006.

Table 4.2 also reveals that the average cost per item for COX-inhibitors demonstrated little change with R74.63 (±72.31) in 2004 to R58.62 (±58.80) in 2005 (d-value=0.22) and R46.34 (±48.44) in 2006 with a d-value of 0.2 from 2005 to 2006. The average cost per item for selective COX-2 inhibitors and Coxibs also did not show significant change with selective COX-2 inhibitors from R73.87 (±54.49) in 2004 to R61.68 (±39.33) in 2005 (d-value=0.22) and R74.23 (±42.05) in 2006 with a d-value of 0.29 from 2005 to 2006, and Coxibs from R242.74 (±135.27) in 2004 to R234.02 (±130.35) in 2005 (d-value=0.06) and R256.27 (±132.70) in 2006 with a d-value of 0.16 from 2005 to 2006.

In 2004 the prevalence of Coxibs (n=47 938) was three and a half times lower (47 %) than that of COX-inhibitors (n=161 306) but the average cost per Coxib item (R242.74 ±135.27) was significantly higher (d-value 1.24) in relation to COX-inhibitors (R74.63 ±72.31). In 2005 the prevalence of Coxibs (n=13 276) decreased more than threefold in comparison with the prevalence of the previous year (n=47 938). This could be related to the providers and public's perception of Coxibs and their related safety after the withdrawal of Vioxx® late in 2004 (Merck, 2004) and other Coxibs such as Bextra® in 2005 (FDA, 2005). In 2006 the prevalence for Coxibs (n=12 355) did not show significant change while the prevalence for Selective COX-2 inhibitors decreased more than twofold in comparison with the prevalence of the previous year (n=19 782).

The percentage of the total prevalence of all NSAIDs according to pharmacological groups is illustrated in figure 4.9, and shows significant changes in pattern during Term 3 and Term 8. During Term 3 the use of medicine items in COX-inhibitors has a sharp increase and then decreases again in Term 8, while the medicine items in Coxibs show a sharp decrease in Term 3 and a significant increase in Term 8 again.

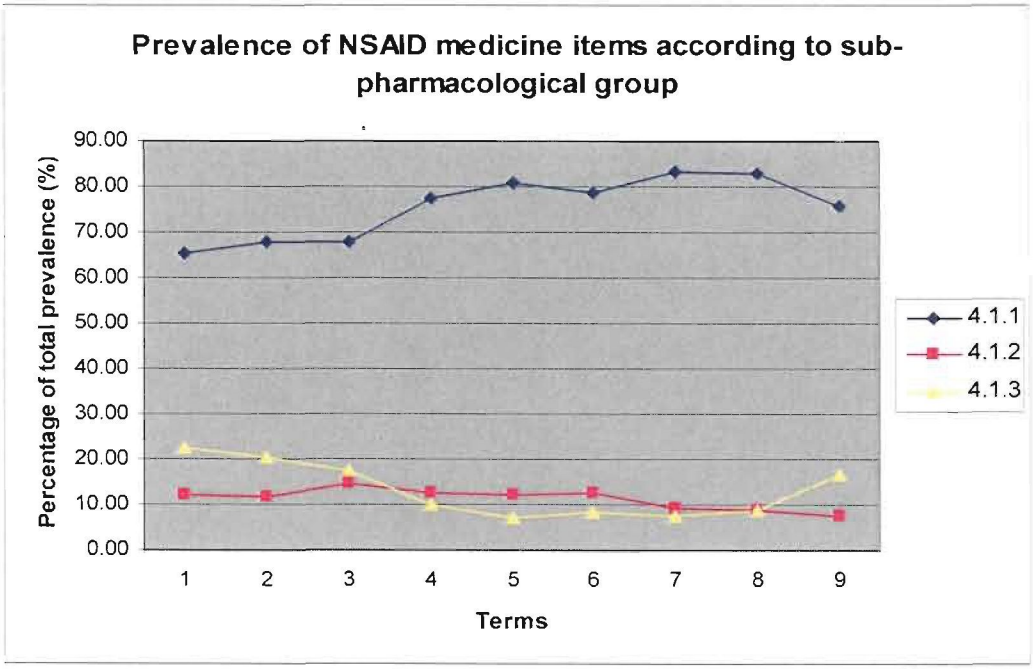

Figure 4.9 The prevalence of NSAID medicine items according to sub-pharmacological group

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)

4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)

4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

Vioxx® (sub-pharmacological group 4.1.3) was removed from the market in Term 3 (Merck, 2004) due to possible dangerous side-effects, while Bextra® (sub-pharmacological group 4.1.3) was removed from the market also due to side-effects in 2005, this could have influenced the public, as well medical prescribers' opinion of all Coxibs and caused a decrease in Coxib use. In 2006 (Term 8), Prexige® was introduced to the South African market and could be responsible for the sudden increase in Coxib use.

According to table 4.2 the cost percentage showed the following changes for COX-inhibitors: 46.41 % (R12 038 915.11); 62.86 % (R7 322 302.78) and 52.06 % (R4 202 815.26) for 2004, 2005 and 2006 respectively. The cost percentage for Selective COX-2 inhibitors was 8.74 % (R2 267 500.21) in 2004, increased to 10.47 % (R1 220 154.74) in 2005 and decreased again to 8.72 % (R703 968.75) in 2006. Similarly Coxibs had a cost percentage of 44.85 % (R11 636 571.50) in 2004, decreased to 26.67 % (R3 106 893.59) in 2005 and increased again to 39.22 % (R3 166 250.73) in 2006. These changes are clearly shown in figure 4.10 below, as well as similar changes in Term 3 and Term 8 as in figure 4.9. These changes can be credited to uncertainty in the market with the withdrawal of Coxibs such as Vioxx® and Bextra® and the introduction of Prexige®.

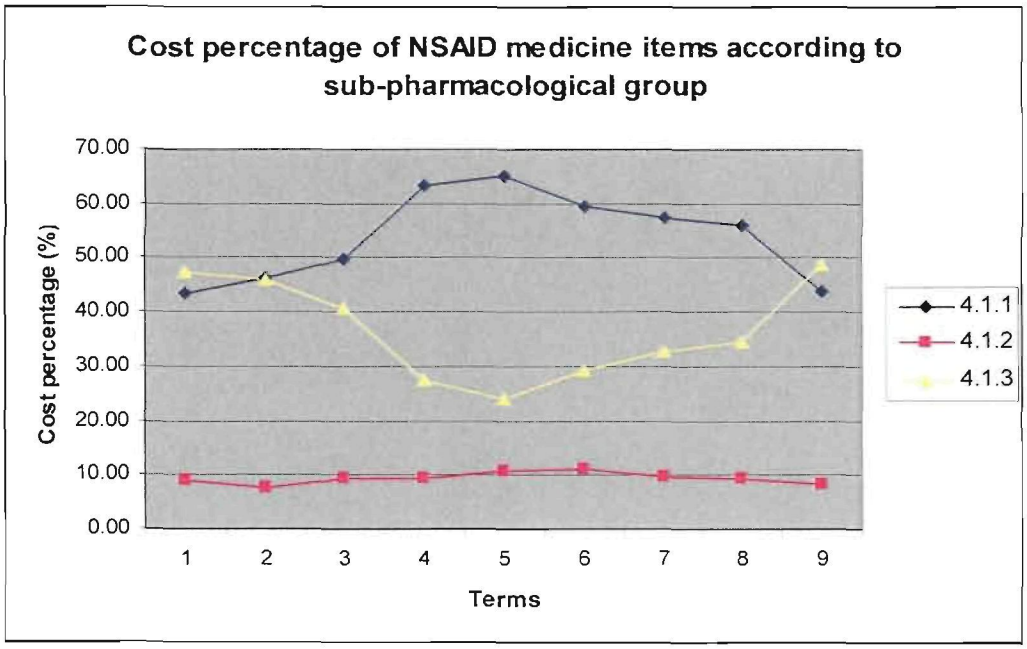

Figure 4.10 The cost percentage of NSAIDs according to sub-pharmacological group to Medicine claim database I

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)

4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)

4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

The (CPI) cost prevalence index (table 4.2) was 0.69 (R12 038 915.11) for COX-inhibitors, 0.68 (R2 267 500.21) for Selective COX-2 inhibitors, and 2.25 (R11 636 571.50) for Coxibs in 2004. In 2005 the CPI for COX-inhibitors was 0.79 (R7 322 302.78), Selective COX-2 inhibitors was 0.84 (R1 220 154.74) while Coxibs increased to 3.17 (R3 106 893.59) during the same year. In 2006 the CPI for COX-inhibitors was 0.65 (R4 202 815.26), Selective COX-2 inhibitors increased to 1.03 (R703 968.75) while Coxibs had a minimal increase to 3.57 (R3 166 250.73) in 2006, thus indicating the relative expensiveness of Coxibs with a CPI higher than one.

4.2.2.3 The prevalence and cost of Coxib medicine items for medicine claim database I

According to table 4.3 the average cost per general medicine item was R124.62 (±228.55) in 2004, R112.51 (±226.99) in 2005, and R117.76 (±237.81) in 2006. The average cost per NSAID medicine item was R108.12 (±109.89) in 2004 and decreased to R73.74 (±81.94) in 2005, and again to R71.73 (±90.73) in 2006. The average cost per Coxib medicine item did not show much change with an average cost per item of R242.74 (±135.27) in 2004, R234.02 (±130.35) in 2005, and R256.27 (±132.70) in 2006. Figure 4.11 (below) demonstrates the average cost per general medicine item, NSAID medicine item and Coxib medicine items from term 1 to term 9. The data show that the average cost of a Coxib medicine item is twice that of the average cost per general medicine item. The average cost per Coxib medicine item took a decline to R192.15 (±113.15) in term 3 and peaked again at R304.99 (±138.66) in term 7.

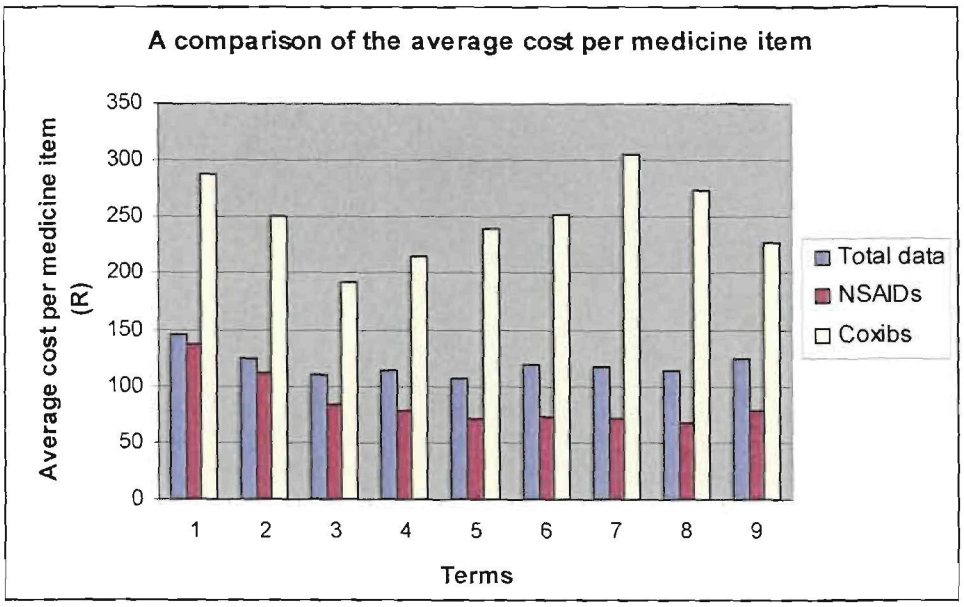

Figure 4.11 A comparison of the average cost per medicine item for Medicine claim database I

The total cost (table 4.3) of all medicine items claimed (Medicine claim database I) for 2004 was R661 221 000.00 (N=5 305 846).

Table 4.3 The prevalence and cost of Coxib medicine items for Medicine claim database I

PREVALENCE AND CPST OF COXIB MEDICINE ITEMS FOR 2004 TO 2006 - MEDICINE CLAIM DATABASE I																
		Total data			NSAID data					Coxib data						
Year	Term	Total number medicine items	Average cost per medicine item (R)	Total cost of medicine items (R)	Total number of NSAID medicine items	Percentage of NSAID medicine items (%)*	Average cost /NSAID item (R)	Total cost of NSAID items (R)	Percentage of the total cost of NSAID medicine items (%)*	Total number of Coxib medicine items	Coxib percentage of all medicine iems (%)*	Coxib percentage of all NSAID medicine iems (%)**	Average cost /Coxib medicine item	Total cost of Coxib items	Coxib medicine items as percentage of total cost (%)*	Coxib medicine items as percentage of total NSAID cost (%)**
2004	1	1363571	145.89 (±283.72)	198933607.00	64132	4.70	136.44 (±126.06)	8750301.85	4.40	14429	1.06	22.50	287.08 (±142.42)	4142320.66	2.08	47.34
	2	1953833	124.23 (±208.03)	242720711.00	87225	4.46	112.36 (±112.16)	9800485.42	4.04	17870	0.91	20.49	251.21 (±132.70)	4489139.99	1.85	45.81
	3	1988442	110.42 (±202.84)	219566683.00	88581	4.45	83.45 (±87.23)	7392199.55	3.37	15639	0.79	17.66	192.15 (±113.15)	3005110.85	1.37	40.65
	Total	5305846	124.62 (±228.55)	661221000.00	239938	4.52	108.12 (±109.89)	25942986.82	3.92	47938	0.90	19.98	242.74 (±135.27)	11636571.50	1.76	44.85
2005	4	1124635	113.12 (±209.13)	127217012.00	51352	4.57	77.33 (±84.63)	3971139.39	3.12	5069	0.45	9.87	214.24 (±134.70)	1086008.33	0.85	27.35
	5	1384135	107.23 (±222.57)	148423312.00	58648	4.24	70.75 (±79.23)	4149614.75	2.80	4133	0.30	7.05	240.41 (±128.25)	993611.62	0.67	23.94
	6	1098222	118.54 (±248.86)	130188773.00	47975	4.37	73.55 (±82.11)	3528596.97	2.71	4074	0.37	8.49	252.15 (±123.54)	1027273.64	0.79	29.11
	Total	3606992	112.51 (±226.99)	405829097.00	157975	4.38	73.74 (±81.94)	11649351.11	2.87	13276	0.37	8.40	234.02 (±130.35)	3106893.59	0.77	26.67
2006	7	778669	117.16 (±227.74)	91226251.18	36048	4.63	70.34 (±90.79)	2535515.34	2.78	2724	0.35	7.56	304.99 (±138.66)	830793.91	0.91	32.77
	8	834501	113.10 (±229.16)	94386321.55	38460	4.61	67.39 (±86.52)	2591776.79	2.75	3292	0.39	8.56	272.72 (±129.91)	897789.63	0.95	34.64
	9	757402	123.51 (±256.44)	93548259.48	38033	5.02	77.45 (±94.46)	2945742.61	3.15	6339	0.84	16.67	226.80 (±123.57)	1437667.19	1.54	48.80
	Total	2370572	117.76 (±237.81)	279160832	112541	4.75	71.73 (±90.73)	8073034.74	2.89	12355	0.52	10.98	256.27 (±132.70)	3166250.73	1.13	39.22

* The number of items and the total cost of items, for both NSAIDs and Coxibs, were calculated as a percentage of the total number of items and total cost of all items, in the medicine claim database.

** The number of Coxib items and the cost of Coxib items, were calculated as a percentage of the total number of NSAID items and the total cost of NSAID items, in the medicine claim database.

NSAID medicine items accounted for 3.92 % (R25 942 986.82) of the total cost of all medicine items claimed during 2004 and Coxib medicine items accounted for 1.76 % (R 11 636 571.50) of the cost of all medicine items. The total cost of all medicine items claimed was R405 829 097.00 (N=3 606 992) in 2005, while NSAID medicine items accounted for only 2.87 % (R11 649 351.11) of the total cost of all medicine items and Coxib medicine items accounted for 0.77 % (R 3 106 892.59) of the cost of all medicine items. The total cost of all medicine items claimed in 2006 was R279 160 83.00 (N=2 370 572), while NSAID medicine items accounted for 2.89 % (R8 073 034.74), and Coxib medicine items accounted for 1.13 % (R 3 166 250.73) of the cost of all medicine items. Figure 4.12 (below) demonstrates the cost percentage of NSAID and Coxib medicine items from term 1 (NSAID= 4.40 %, Coxib= 2.08 %) to term 9 (NSAID= 3.15 %, Coxib= 1.54 %).

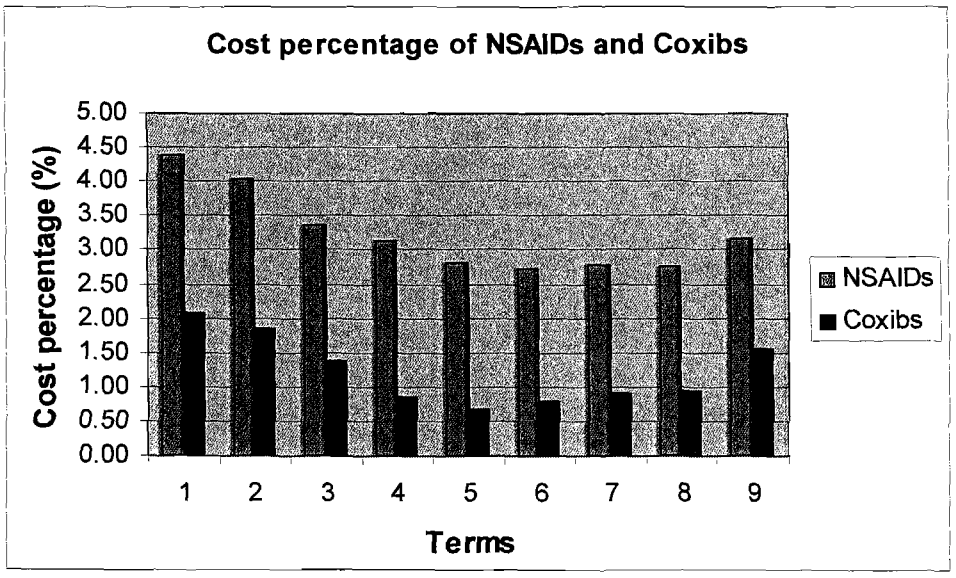

Figure 4.12 The cost percentage of NSAID and Coxib medicine items for medicine claim database I

Coxib medicine items accounted for almost half [44.85 %, (R11 636 571.50)] of all NSAID costs in 2004. This number decreased to 26.67 % (R3 106 893.59) in 2005, and can be seen in figure 4.12, where the comparative trends of NSAID and Coxib cost percentages over the three-year period are shown. In 2006 there was an increase, and Coxib medicine items accounted for 39.22 % (R3 166 250.73) of all NSAID costs. The total cost of all medicine items, NSAID medicine items and Coxib medicine items, showed a decrease over the three-year period. This decrease in total cost can be due to the decrease in the total number of items claimed (table 4.3) during each year from 2004 to 2006. The total number of medicine items claimed (Medicine claim database I) decreased more than twofold from 2004 (N=5 305 846) to 2006 (N=2 370 572), whilst NSAID medicine items claimed for the same period also decreased

twofold from 239 938 NSAID items in 2004 to 112 541 NSAID medicine items claimed in 2006. However, Coxib medicine items showed the greatest change in prevalence of items claimed by decreasing almost fourfold from 47 938 Coxib items claimed in 2004 to 12 355 Coxib items claimed in 2006. This might be due to the change in the number of medical schemes processed by Medicine claim database I from 80 to 68 from 2004 to 2005, and from 68 to 35 from 2005 to 2006.

4.2.3 Summary for medicine claim database I

- Between 9 % and 10.5 % of all prescriptions dispensed through Medicine claim database I during the study period were NSAID prescriptions.
- NSAID medicine items represented an average of 4.5 % of all medicine items during the study period.
- The average cost per medicine item decreased from R124.62 (±228.55) in 2004 to R117.76 (±237.81) in 2006 while the average cost per NSAID medicine item decreased from R108.12 (±109.89) in 2004 to R71.73 (±90.73) in 2006.
- NSAID medicine items represented between 3.9 % and 2.9 % of the cost of all medicine items during the study period.
- The prevalence of Coxibs (sub-pharmacological group 4.1.3) decreased significantly from almost 20 % in 2004 to 8.4 % in 2005, and almost 10.9 % in 2006.
- In 2004 the prevalence of Coxibs (n=47 938) was 47 per cent lower than that of COX-inhibitors (n=161 306) while the average cost per Coxib item (R242.74 ±135.27) was significantly higher (d-value 1.24) than that of COX-inhibitors (R74.63 ±72.31).
- In 2005 the prevalence of Coxibs (n=13 276) decreased approximately 11 per cent in comparison with the prevalence of the previous year (n=47 938).
- The prevalence of both COX-inhibitors (sub-pharmacological group 4.1.1), and Coxibs (sub-pharmacological group 4.1.3) demonstrated a change in term 3 when COX-inhibitors showed an increase in use, while Coxibs showed and almost equal but opposite trend with a decrease in use.
- The cost percentage for COX-inhibitors demonstrated opposite trends from that of Coxibs with a peak during term 5, while Coxibs demonstrated a dip during the same term.
- COX-inhibitors and Selective COX-2 inhibitors were relatively inexpensive with a CPI of one or below during the study period, while Coxibs were relatively expensive with a CPI above one during the study period.

- The average cost per Coxib medicine item was twice that of the average cost per general medicine item, and took a decline in term 3 while it peaked again in term 7.
- Coxib medicine items accounted for almost half [44.85 %, (R11 636 571.50)] of all NSAID costs in 2004, which decreased to 26.67 % and 39.22 % in 2005 and 2006 respectively, due to the decrease in the percentage of Coxib prevalence during these years.
- The prevalence of Coxib medicine items claimed decreased with approximately 9 % from 2004 to 2006.

4.3 DISCUSSION OF THE RESULTS FOR MEDICINE CLAIM DATABASE M

4.3.1 Notes related to the interpretation of the results

For the purpose of this study, each year will consist of three time periods. In total there will be 6 time periods. The first study year consists of Term 4, Term 5 and Term 6, and the second study year consists of Term 7, Term 8 and Term 9. This is to make provision for easier comparisons between Medicine claim database I and Medicine claim database M.

The time periods will be as follows:

Term 4	1 January 2005 to 30 April 2005
Term 5	1 May 2005 to 31 August 2005
Term 6	1 September 2005 to 31 December 2005
Term 7	1 January 2006 to 30 April 2006
Term 8	1 May 2006 to 31 August 2006
Term 9	1 September 2006 to 31 December 2006

- Some of the tables will not add up to one hundred per cent because percentages were rounded off to two decimals.
- Some of the tables will not add up perfectly because in some cases the data that we received rounded their totals off to the nearest rand while others rounded their totals of to two decimals.
- In the medicine claim database M the cost amounts for Bextra® were possibly provided "incorrectly" with total costs for Bextra® no more than a few cents. This could not be changed and will show in the data.
- The effect sizes (d-values) were calculated and described in the text, but not indicated in any tables.

- The total cost and prevalence for NSAID medicine items per year do not correlate with the sum of the cost and prevalence for the male and female groups for NSAID medicine items for the same year due to the unknown gender group on the medicine claim database, that was not included in the tables.
- For the purpose of this study, an anti-inflammatory drug (NSAID) prescription, is any prescription that contains one or more NSAID items.
- For the purpose of this study, a general prescription, is any prescription that contains one or more medicine items.
- Due to the nature and extent of the study, with reference to the general and specific objectives (refer to paragraphs 1.3.1 & 1.3.2) to investigate the related usage and cost patterns of the active ingredients of NSAIDs, the effect of possible substitution of generic equivalents were not investigated. This may have an influence on cost-related aspects and may be seen as a limitation of the study.
- The standard deviations for average cost were indicated in the relevant tables but not shown in any figures. The standard deviations for the averages in figure 4.13 and figure 4.15 were indicated in table 4.4, while the standard deviations for the averages in figure 4.20 were indicated in table 4.7.
- Due to technical reasons the size and font of the text and tables may differ.

4.3.2 General analysis for Medicine claim database M for the years 2005 and 2006

4.3.2.1 The cost and prevalence of NSAID medicine items

Table 4.4 shows the prescribing patterns of all the medicine items in the total medicine claim database, as well as all the NSAID medicine items, for the two study years, 1 January 2005 to 31 December 2005, and 1 January 2006 to 31 December 2006.

Table 4.4 shows that 10.31 % (n=879 065) of the total number of prescriptions (N=8 522 574) dispensed according to Medicine claim database M for the period 1 January 2005 to 31 December 2005, were NSAID prescriptions. The percentage of NSAID prescriptions decreased during the next year (period 1 January 2006 to 31 December 2006) to 9.99 % (n=903 983). Over a two-year period the percentage of NSAID prescriptions decreased from 10.31 % in 2005 to 9.99 % in 2006 while the total number of NSAID prescriptions increased over the same period from 879 065 prescriptions in 2005 to 903 983 in 2006. The total number of general prescriptions also increased from 8 522 574 in 2005 to 9 046 138 in 2006. Whilst the total number of general prescriptions according to table 4.4 increased from 2005 to 2006, the average number of medicine items per prescription was at an average of 2.33 (±1.56) medicine items per

Table 4.4 The cost and prevalence of all medicine items for Medicine claim database M (2005 – 2006)

COST AND PREVALENCE OF ALL MEDICINE ITEMS DURING 2005 TO 2006 FOR MEDICINE CLAIM DATABASE M																
		Total data						NSAID data								
Year	Term	Total number of Rx	Average number of medicine items /Rx	Average cost / Rx (R)	Total number of medicine items	Average cost/ medicine item (R)	Total Cost of all medicine items (R)	Total number NSAID Rx's	Percent-age total number NSAID Rx (%)*	Average number of NSAID medicine items /Rx	Average cost /NSAID Rx (R)	Total number of NSAID items	Percent-age total number of NSAID medicine items (%)*	Average cost /NSAID medicine item (R)	Total cost of NSAID medicine items (R)	Percent-age of total cost of NSAID medicine items (%)
2005	4	2622641	2.29 (±1.56)	223.94 (±402.99)	6005321	97.80 (±178.65)	587305503.00	280542	10.70	1.04 (±0.22)	71.93 (±77.92)	293202	4.88	68.82 (±73.74)	20179291.69	3.44
	5	3095256	2.37 (±1.56)	218.26 (±483.62)	7332627	92.13 (±192.92)	675587370.00	312456	10.09	1.05 (±0.22)	63.68 (±72.54)	327063	4.46	60.83 (±68.39)	19896752.38	2.95
	6	2804677	2.33 (±1.56)	224.80 (±491.69)	6522645	96.66 (±203.11)	630484048.00	286067	10.20	1.05 (±0.24)	63.67 (±72.0)	301598	4.62	60.39 (±67.60)	18214368.48	2.89
	Total	8522574	2.33 (±1.56)	222.16 (±463.13)	19860679	95.33 (±192.21)	1893376921.00	879065	10.31	1.05 (±0.23)	66.31 (±74.23)	921863	4.64	63.23 (±69.80)	58290412.55	3.08
2006	7	2998035	2.33 (±1.56)	222.91 (±527.68)	6984380	95.68 (±215.17)	668291742.00	306174	10.21	1.05 (±0.24)	63.35 (±71.04)	322857	4.62	60.07 (±67.21)	19395803.95	2.90
	8	3313736	2.43 (±1.58)	221.60 (±549.32)	8048497	91.24 (±219.18)	734323606.00	327741	9.89	1.06 (±0.24)	60.50 (±69.79)	346050	4.30	57.30 (±66.15)	19827697.63	2.70
	9	2734367	2.35 (±1.60)	235.64 (±597.58)	6440185	100.05 (±251.03)	644329035.00	270068	9.88	1.06 (±0.24)	68.61 (±76.52)	285334	4.43	64.94 (±71.24)	18528765.44	2.88
	Total	9046138	2.37 (±1.58)	226.28 (±557.49)	21473074	95.33 (±227.98)	2046944383.00	903983	9.99	1.06 (±0.24)	63.89 (±72.35)	954241	4.44	60.52 (±68.13)	57752267.02	2.82

**Rx refers to prescription

* The number of NSAID prescriptions and number of NSAID items, according to terms and years, were calculated as a percentage of the total number of prescriptions and total number of items in the medicine claim database.

prescription in 2005, and an average of 2.37 (±1.58) medicine items per prescription in 2006 (d- value 0.02). The average number of NSAID medicine items per prescription showed no significant change with 1.05 (±0.23) NSAID medicine items per prescription in 2005, and 1.06 (±0.24) NSAID medicine items per prescription in 2006 (d-value 0.04).

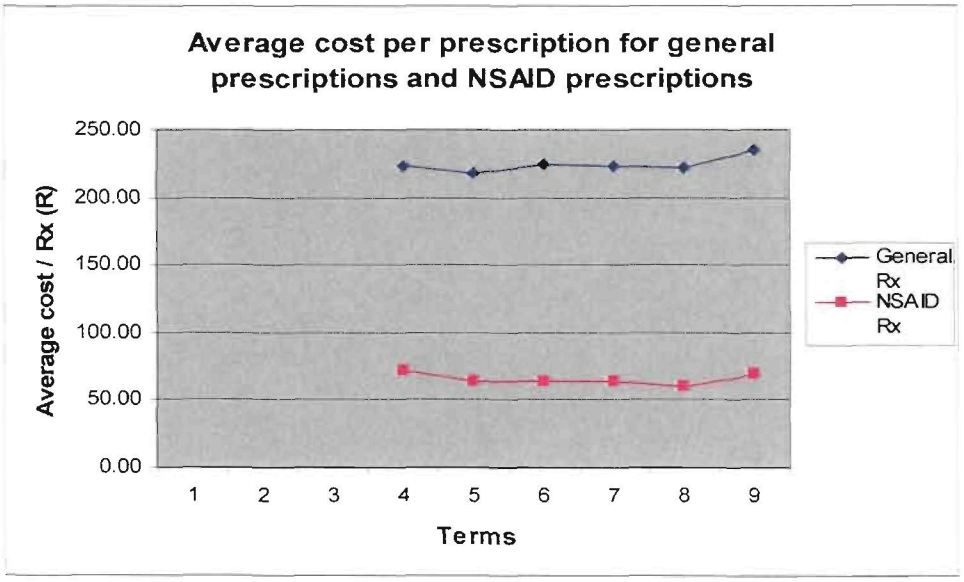

Figure 4.13 The average cost per prescription for Medicine claim database M

The average cost per general prescription according to table 4.4 indicates insignificant changes from R222.16 (±463.13) in 2005, to R226.28 (±557.49) in 2006 (d-value 0.01). The average cost per NSAID prescription decreased from R66.31 (±74.23) in 2005 to R63.89 (±72.35) in 2006 (d-value 0.03). The average cost per NSAID prescription for Term 4 (R71.93 ±77.92) through to Term 9 (R68.61 ±76.52) is presented in figure 4.13. This figure represents the average cost per prescription for Medicine claim database M and shows similar trends for average cost per NSAID prescription [d-values 0.13 (2005), and d-value 0.14 (2006)] as figure 4.5, which illustrates the average cost per prescription for Medicine claim database I. While both these figures (figure 4.5, figure 4.13) demonstrate a similar trend in cost per NSAID prescription for term 4 to term 9, the average cost per general prescription varies significantly. The average cost per general prescription for medicine claim database I (figure 4.5) is higher than that of medicine claim database M (figure 4.13), which remains below an average cost of R250.00 per prescription. The average cost per general prescription for Medicine claim database I (figure 4.5) also demonstrates an increase in cost from term 6 to term 9.

According to table 4.4 the percentage of NSAID medicine items is 4.64 % (n=921 863) of all medicine items (N=19 860 679) for 2005, decreasing to 4.44 % (n=954 241) of all medicine items (N=21 473 074) in 2006. Figure 4.14 illustrates the changes in percentage of NSAID

medicine items over the two-year period, starting with a 4.88 % (n=293 202) of NSAID medicine items in Term 4 through to 4.43 % (n=954 241) in Term 9.

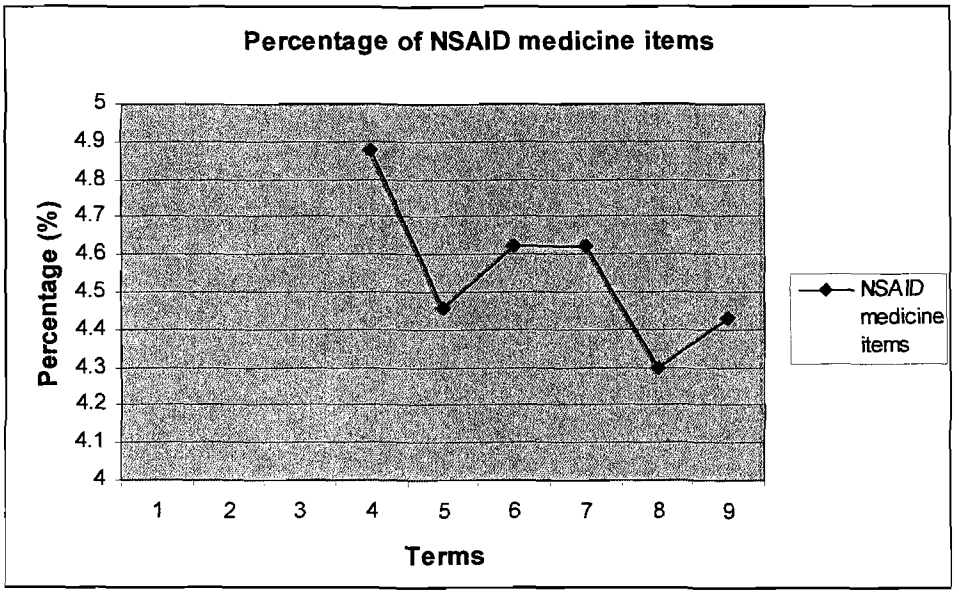

Figure 4.14 The percentage of NSAID medicine items for Medicine claim database M for 2005 and 2006.

The percentage of medicine items claimed according to medicine claim database M (figure 4.14) and medicine claim database I (figure 4.6) shows differences in percentage possibly due to the changes in the total number of medicine items claimed for each medicine claim database during the study period.

Table 4.4 shows the average cost per medicine item remaining constant at R95.33 (±192.21) in 2005, and R95.33 (±227.98) in 2006. The average cost per NSAID medicine item showed a decrease from R63.23 (±69.80) in 2005, to R60.52 (±68.13) in 2006. The figure 4.15 shows the decrease of the average cost per NSAID medicine item from Term 4 (R68.82 ±73.74) to Term 9 (R64.94 ±71.24). There is a slow but steady decrease in average cost per NSAID medicine item from Term 4 to Term 8, with a sudden increase in Term 9 to R64.94 (±71.24). This shows a similar trend to the average cost per NSAID medicine item for medicine claim database I (figure 4.7), and as stated above in the discussion of table 4.1 and figure 4.7 (refer to paragraph 4.2.2.1), this increase can possibly be attributed to the contributions of Prexige® (lumiracoxib), a new Coxib medicine item. This sudden increase in Term 9 can be attributed to lumiracoxib that had an average cost of R187.51 (±108.36) in Term 9 for medicine claim database I (Appendix B, table B.1.1), and an average cost of R129.75 (±77.16) in Term 9 for medicine claim database M (Appendix B, table B.2.1), and was released on the South African market April 2006 (South Africa, 2006).

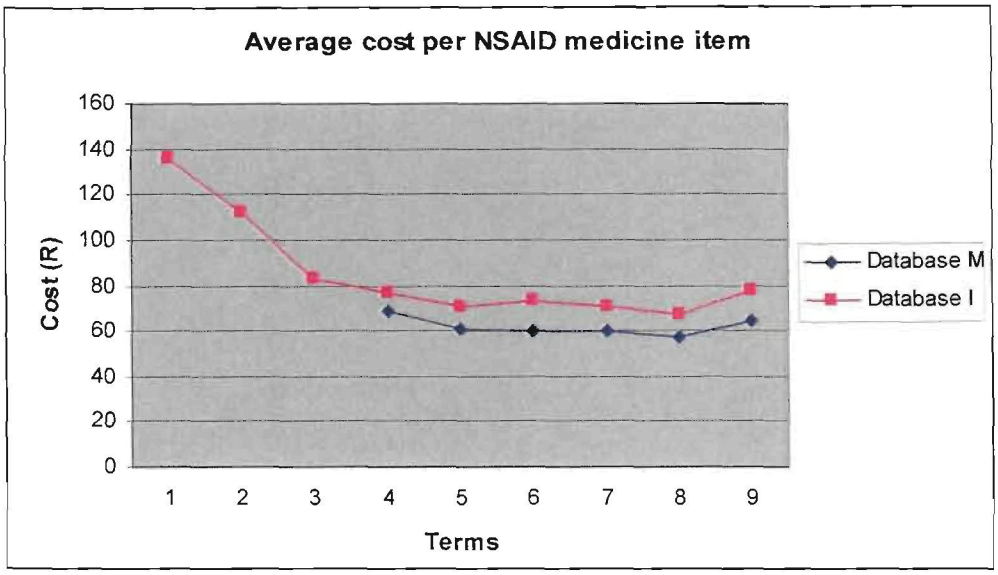

Figure 4.15 The average cost per NSAID medicine item for Medicine claim databases I and M.

According to table 4.4 the total cost of all NSAID medicine items amounted to R58 290 412.55 (n=921 863) in 2005, and decreased to R57 752 267.02 (n=954 241) in 2006. The percentage of the total cost of NSAID medicine items was determined (table 4.4) and is shown in figure 4.16. The cost percentages of NSAID medicine items were 3.08 % in 2005, and 2.82 % in 2006. According to Mediscor's 2006 medicine review, NSAIDs as therapeutic group was ranked fifth in 2004, behind other therapeutic groups such as anti-hypertensives, hipolididaemics, anti-depressants and sex hormones, and ranked seventh and eighth in 2005 and 2006 respectively (Bester, 2007:8).

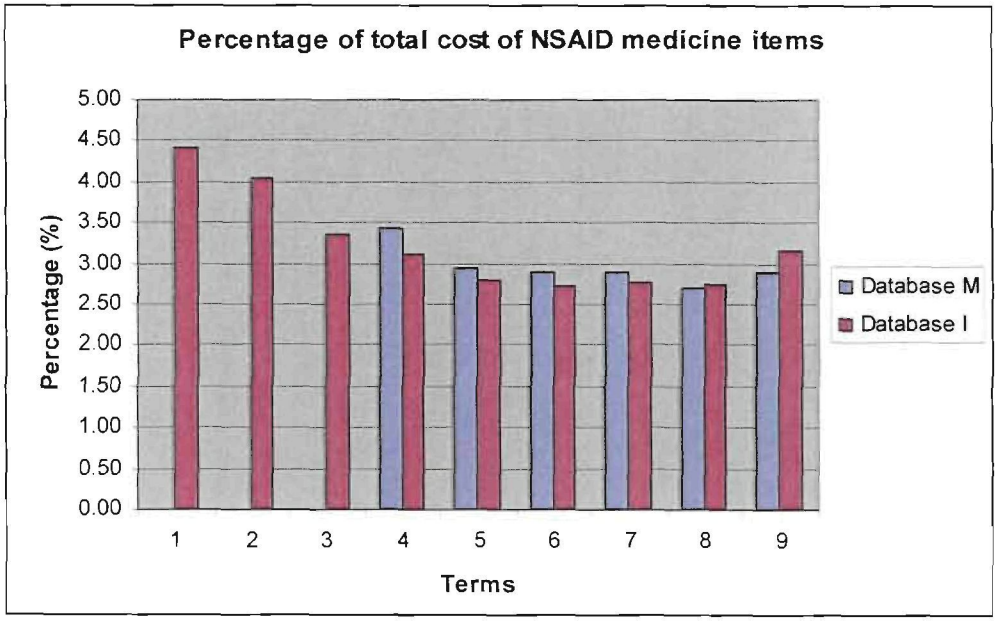

Figure 4.16 The percentage of total costs of NSAID medicine items for Medicine claim databases M and I

4.3.2.2 The prevalence of different sub-pharmacological groups for Medicine claim database M

According to table 4.5 the percentage of total prevalence of COX-inhibitors (sub-pharmacological group 4.1.1) was 72.41 % (n=667 556) in 2005, decreasing to 70.87 % (n=676 292) in 2006. The percentage of total prevalence of selective COX-2 inhibitors (sub-pharmacological group 4.1.2) indicated little change with an increase from 17.69 % (n=163 043) in 2004 to 18.17 % (n=173 339) in 2005. The percentage of total prevalence of Coxibs (sub-pharmacological group 4.1.3) showed a similar trend to that of medicine claim database I (refer to paragraph 4.2.2.2) with an increase from 9.90 % (n=91 264) in 2005 to 10.96 % (n=104 610) in 2006. The average cost per item (table 4.5) for COX-inhibitors did not display significant change from R45.12 (±50.03) in 2005 to R40.79 (±46.95) in 2006 (d-value= 0.08). The average cost per selective COX-2 inhibitor also did not indicate significant change with R60.36 (±37.69) in 2005 and R62.02 (±37.49) in 2006 (d-value= 0.04). The average cost per Coxib item was R200.80 (±83.89) in 2005 and it decreased to R185.56 (±87.27) in 2006 (d-value= 0.17).

Table 4.5 The prevalence of sub-pharmacological groups for Medicine claim database M

PREVALENCE OF DIFFERENT SUB-PHARMACOLOGICAL GROUPS FOR MEDICINE CLAIM DATABASE M 2005-2006								
Year	**Term**	**Sub-pharmacological group**	**Prevalence (n)**	**Percentage of total prevalence (%) ***	**Average cost (R)**	**Total cost (R)**	**Cost percentage (%) ***	**Cost prevalence index ****
2005	**4**	4.1.1	202141	68.94	48.71 (±52.92)	9846170.29	48.79	0.71
		4.1.2	53498	18.25	60.11 (±37.88)	3215617.47	15.94	0.87
		4.1.3	37563	12.81	189.48 (±88.58)	7117503.93	35.27	2.75
	5	4.1.1	243688	74.51	44.30 (±49.60)	10796172.26	54.26	0.73
		4.1.2	55741	17.04	59.73 (±37.85)	3329330.12	16.73	0.98
		4.1.3	27634	8.45	208.85 (±80.35)	5771250.00	29.01	3.43
	6	4.1.1	221727	73.52	42.76 (±47.53)	9480978.04	52.05	0.71
		4.1.2	53804	17.84	61.27 (±37.30)	3296560.20	18.10	1.01
		4.1.3	26067	8.64	208.57 (±78.58)	5436830.24	29.85	3.45
	Total	4.1.1	667556	72.41	45.12 (±50.03)	30123320.59	51.68	0.71
		4.1.2	163043	17.69	60.36 (±37.69)	9841507.79	16.88	0.95
		4.1.3	91264	9.90	200.80 (±83.89)	18325584.17	31.44	3.18

Table 4.12 (continued)

Year	Term	Sub-pharmacological group	Prevalence (n)	Percentage of total prevalence (%) *	Average cost (R)	Total cost (R)	Cost percentage (%) *	Cost prevalence index **
2006	7	4.1.1	235266	72.87	42.62 (±47.88)	10027006.16	51.70	0.71
		4.1.2	60489	18.74	61.96 (±37.50)	3747897.02	19.32	1.03
		4.1.3	27102	8.39	207.40 (±80.07)	5620900.77	28.98	3.45
	8	4.1.1	253146	73.15	39.23 (±45.77)	9929885.41	50.08	0.68
		4.1.2	60856	17.59	61.56 (±37.16)	3746471.02	18.90	1.07
		4.1.3	32048	9.26	191.94 (±85.68)	6151341.20	31.02	3.35
	9	4.1.1	187880	65.85	40.62 (±47.25)	7632406.91	41.19	0.63
		4.1.2	51994	18.22	62.64 (±37.84)	3257026.64	17.58	0.96
		4.1.3	45460	15.93	168.04 (±88.93)	7639331.89	41.23	2.59
	Total	4.1.1	676292	70.87	40.79 (±46.95)	27589298.48	47.77	0.67
		4.1.2	173339	18.17	62.02 (±37.49)	10751394.68	18.62	1.02
		4.1.3	104610	10.96	185.56 (±87.27)	19411573.86	33.61	3.07

* The number of NSAID items and cost of NSAID items, per sub-pharmacological group, were calculated as a percentage of the total number of items, and total cost of all items in the medicine claim database, in terms as well as years.

** Refer to paragraph 3.5.2.3

In 2005 the prevalence of Coxibs (n=91 264) was approximately 62 % lower than that of COX-inhibitors (n=667 556) but the average cost per Coxib item (R200.80 ±83.89) was significantly higher (d-value 1.85) in relation to COX-inbibitors (R45.12 ±50.03).

The percentage of total cost for all NSAID medicine items according to pharmacological groups for Medicine claim database M is illustrated in figure 4.17, and it exhibits similar trends to that of Medicine claim database I (figure 4.9), with a decrease in Coxib items (sub-pharmacological group 4.1.3) dispensed in term 5, that increases again in term 9. COX-inhibitors (sub-pharmacological group 4.1.1) show the opposite of Coxibs, with an increase in term 5, that decreases again in term 9 (figure 4.17). The selective COX-2 inhibitors as shown in figure 4.17 remain approximately unchanged. Figures 4.9 and 4.17 illustrate that the trends in NSAID use are similar in both Medicine claim database I (refer to paragraph 4.2.2.2) and Medicine claim

database M. Bextra® (sub-pharmacological group 4.1.3) was removed from the market due to side-effects in 2005. This could have influenced the public, as well medical prescribers' opinion of all Coxibs and could be responsible for the decrease in Coxib use from term 5 to term 8, consequently substituting Coxib medicine items with COX-inhibitors. In 2006 Prexige® was introduced to the South African market and is possibly responsible for the sudden increase in Coxib medicine use from term 8 to term 9, as similarly shown in figure 4.9.

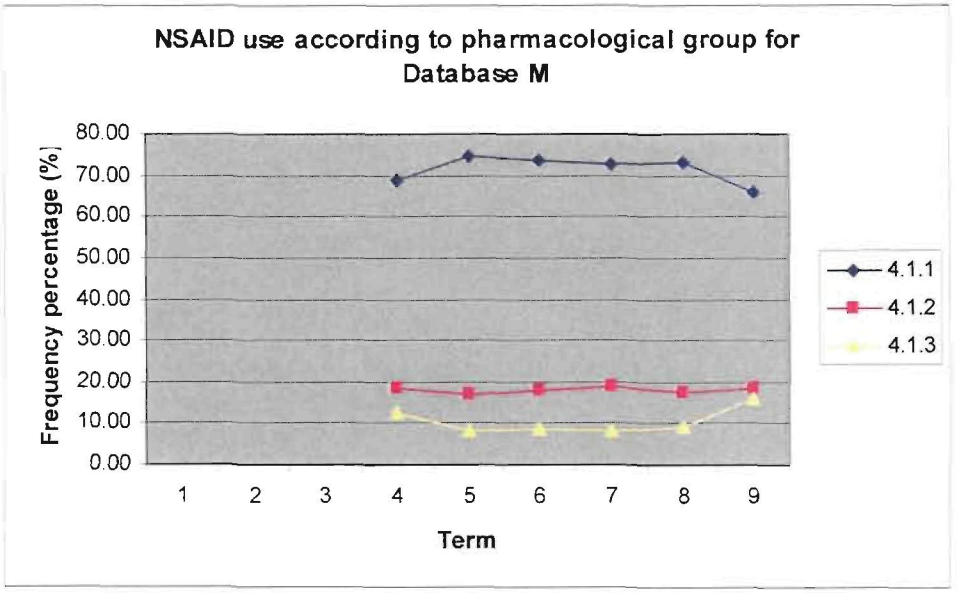

Figure 4.17 The usage of NSAID medicine items according to pharmacological group

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)
4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)
4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

According to table 4.5 the cost percentage showed the following changes for COX-inhibitors: 51.68 % (R30 123 320.59) and 47.77 % (R27 589 298.48) for 2005 and 2006 respectively. The cost percentage for Selective COX-2 inhibitors was 16.88 % (R9 841.507) in 2005 and increased to 18.62 % (R10 751 394.68) in 2006. Similarly Coxibs had a cost percentage of 31.44 % (R18 325 584.17) in 2005 and 33.61 % (R19 411 573.86) in 2006.

These changes are clearly shown in figure 4.18 (below), and show the same trends as figure 4.10 (medicine claim database I). Sub-pharmacological groups 4.1.1 and 4.1.3 are mirror images of each other and suggest that when patients were no longer prescribed Coxib medicine items they were given COX-inhibitors instead. This could be influenced by uncertainty in the market with the withdrawal of Coxibs such as Vioxx® and Bextra® and the introduction of Prexige® in 2006.

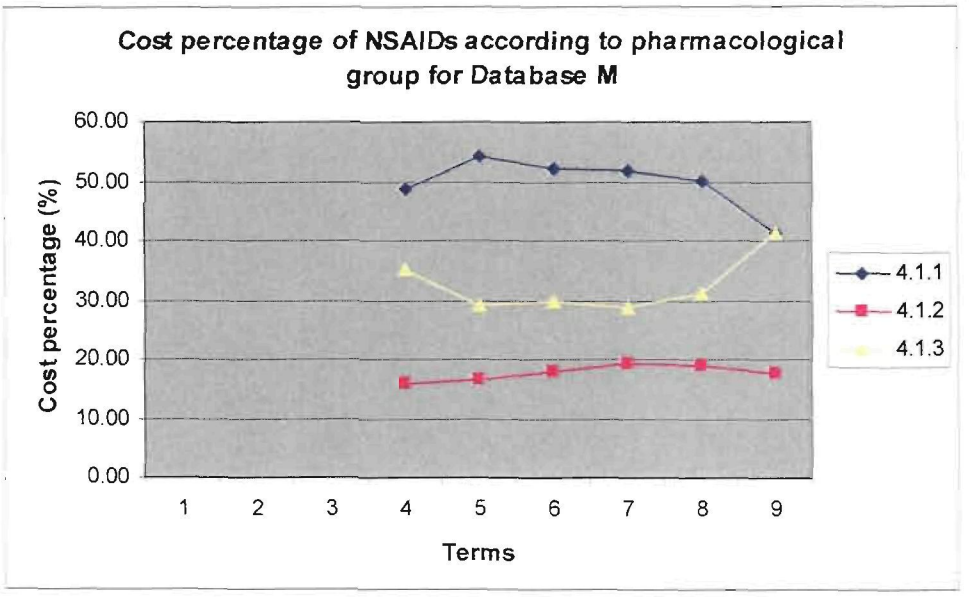

Figure 4.18 The cost percentage of NSAIDs according to sub-pharmacological group for Medicine claim database M

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)
4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)
4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

The (CPI) cost prevalence index (table 4.5) was 0.71 (R9 408 978.04) for COX-inhibitors, 1.01 (R3 296 560.20) for Selective COX-2 inhibitors, and 3.45 (R5 436 830.24) for Coxibs in 2005. The CPI for COX-inhibitors decreased to 0.67 (R27 589 298.48) in 2006 and Selective COX-2 inhibitors was 1.02 (R10 751 394.68) while Coxibs decreased to 3.07 (R19 411 573.86) in 2006.

4.3.2.3 Comparison of the prevalence and cost of sub-pharmacological groups for medicine claim database I and medicine claim database M

Table 4.6 (below) compared the prevalence and cost of the two Medicine claim databases discussed in this study, and indicated that Medicine claim database M processed almost six times as many NSAID medicine items as Medicine claim database I in 2005, and thus accounted for five times as much of cost regarding NSAID medicine items. In 2006 Medicine claim database M had an NSAID prevalence eight and a half times higher than that of Medicine claim database I, accounting for seven times the cost of Medicine claim database I for NSAID medicine items. Figure 4.19 depicts the total costs for both medicine claim databases for both 2005 and 2006 according to sub-pharmacological groups.

Table 4.6 A comparison of the prevalence and cost of sub-pharmacological groups for Medicine claim database I and Medicine claim database M

Comparison of the prevalence and cost of sub-pharmacological groups for Medicine claim database I and Medicine claim database M								
YEAR	TERM	Sub-pharmaco-logical group	DATABASE I			DATABASE M		
			Prevalence (n)	Total cost (R)	Cost prevalence index	Prevalence (n)	Total cost (R)	Cost prevalence index *
2005	4	4.1.1	39802	2511890.10	0.82	202141	9846170.29	0.71
		4.1.2	6481	373240.96	0.74	53498	3215617.47	0.87
		4.1.3	5069	1086008.33	2.77	37563	7117503.93	2.75
	5	4.1.1	47305	2706664.17	0.81	243688	10796172.26	0.73
		4.1.2	7210	449338.96	0.88	55741	3329330.12	0.98
		4.1.3	4133	993611.62	3.40	27634	5771250.00	3.43
	6	4.1.1	37810	2103748.51	0.76	221727	9480978.04	0.71
		4.1.2	6091	397574.82	0.89	53804	3296560.20	1.01
		4.1.3	4074	1027273.64	3.43	26067	5436830.24	3.45
	Total	4.1.1	124917	7322302.78	0.79	667556	30123320.59	0.71
		4.1.2	19782	1220154.74	0.84	163043	9841507.79	0.95
		4.1.3	13276	3106893.59	3.17	91264	18325584.17	3.18
Total Year 2005			157975	11649351.11	0.65	921863	58290412.55	0.66
2006	7	4.1.1	30009	1460291.99	0.69	235266	10027006.16	0.71
		4.1.2	3315	244429.44	1.05	60489	3747897.02	1.03
		4.1.3	2724	830793.91	4.33	27102	5620900.77	3.45
	8	4.1.1	31872	1454232.13	0.68	253146	9929885.41	0.68
		4.1.2	3296	239755.03	1.08	60856	3746471.02	1.07
		4.1.3	3292	897789.63	4.05	32048	6151341.20	3.35
	9	4.1.1	28821	1288291.14	0.58	187880	7632406.91	0.63
		4.1.2	2873	249784.28	1.12	51994	3257026.64	0.96
		4.1.3	6339	1437667.19	2.93	45460	7639331.89	2.59
	Total	4.1.1	90702	4202815.26	0.65	676292	27589298.48	0.67
		4.1.2	9484	703968.75	1.03	173339	10751394.68	1.02
		4.1.3	12355	3166250.73	3.57	104610	19411573.86	3.07
Total Year 2006			112541	8073034.74	0.61	954241	57752267.02	0.63

* Refer to paragraph 3.5.2.3

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)

4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)

4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

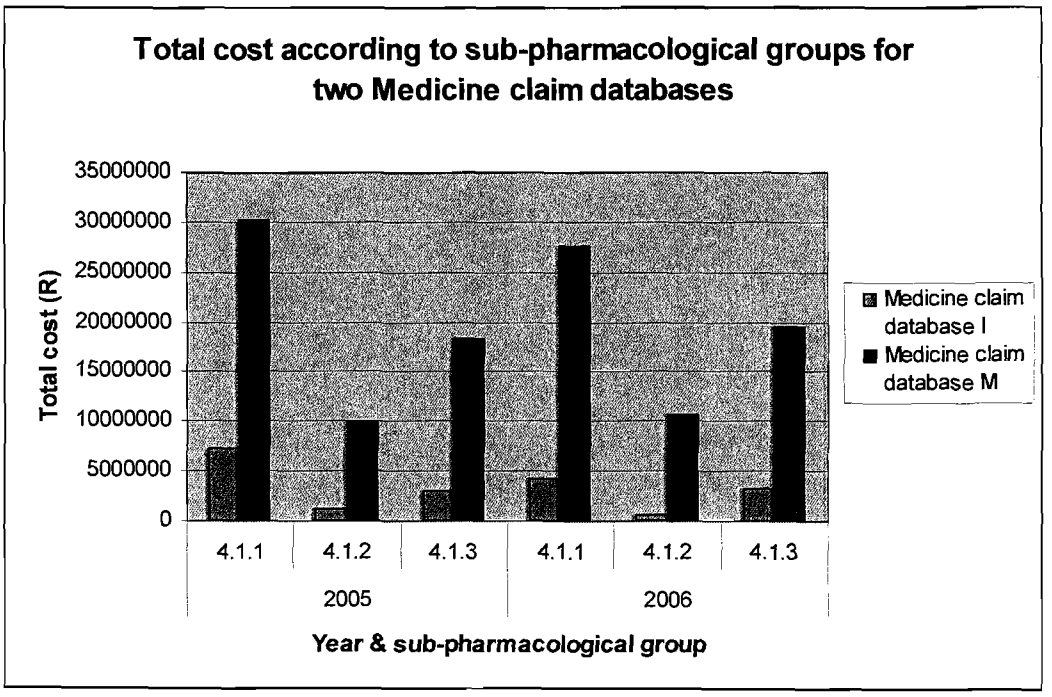

Figure 4.19 Total cost according to sub-pharmacological groups for Medicine claim database I and Medicine claim database M during 2005 and 2006

* 4.1.1 = sub-pharmacological group 4.1.1 (COX-inhibitors)
4.1.2 = sub-pharmacological group 4.1.2 (Selective COX-2 inhibitors)
4.1.3 = sub-pharmacological group 4.1.3 (Coxibs)

The CPI for all NSAIDs for 2005 and 2006 is approximately 0.6 for both medicine claim databases and indicates that NSAIDs as a group are relatively inexpensive. The CPI for COX-inhibitors and Selective COX-2 inhibitors was respectively below one, and approximately one, for both medicine claim databases for both years of the study period, indicating relative inexpensiveness (CPI < 1) and an equilibrium between cost and prevalence (CPI = 1). However, Coxibs according to both databases, had a CPI higher than three for 2005 and 2006, indicating them to be relatively expensive.

4.3.2.4 The prevalence and cost of Coxib medicine items for medicine claim database M

According to table 4.7 the average cost per general medicine item remained the same at (R95.33 ±192.21) and (R95.33 ±227.98) in 2005 and 2006 respectively. However, the average cost per general medicine item for Medicine claim database M was 15.3 % lower than that of Medicine claim database I (table 4.3) in 2005, and 19.0 % lower than that of Medicine claim database I (table 4.3) in 2006. The average cost per NSAID medicine item was R63.23 (±69.80) in 2005 and decreased to R60.52 (±68.13) in 2006. The average cost per Coxib medicine item had an average cost per item of R200.80 (±83.89) in 2005, and R205.46 (±81.87) in 2006. The

average cost per Coxib medicine item for Medicine claim database M was 14.2 % lower than that of Medicine claim database I (table 4.3) in 2005, and 19.8 % lower than that of Medicine claim database I (table 4.3) in 2006. Figure 4.20 (below) demonstrates the average cost per general medicine item, NSAID medicine item and Coxib medicine items term 4 to term 9. This figure (figure 4.20) can be compared with the corresponding figure for Medicine claim database I (figure 4.11). The data show that the average cost of a Coxib medicine item is approximately twice that of the average cost per general item. This coincides with the data from figure 4.11 and table 4.3 (refer to paragraph 4.2.2.3).

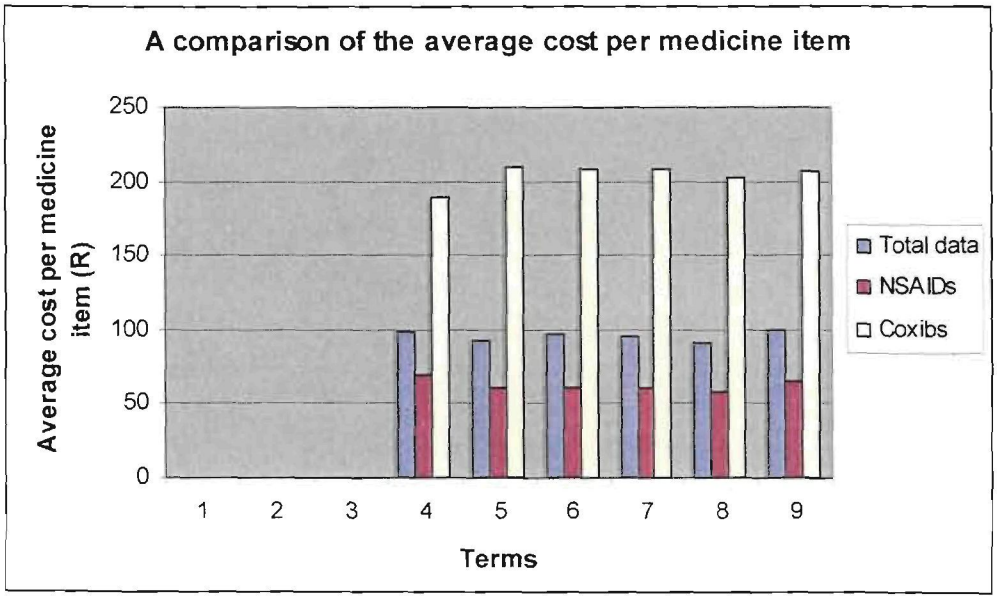

Figure 4.20 A comparison of the average cost per medicine item for Medicine claim database M

The total cost (table 4.7) of all medicine item claims processed by Medicine claim database M for 2005 was R1 893 376 921.00 (N=19 860 679). NSAID medicine items accounted for 3.08 % (R58 290 412.55) of the total cost of all medicine items for 2005 and Coxib medicine items accounted for 0.97 % (R18 325 584.17) of the cost of all medicine items for 2005. The total cost of all medicine items claimed was R2 046 944 383.00 (N=21 473 074) in 2006, while NSAID medicine items accounted for 2.82 % (R57 752 267.02) of the total cost of all medicine items and Coxib medicine items accounted for 0.95 % (R19 411 573.86) of the cost of all medicine items for 2006. Figure 4.21 demonstrates the cost percentage of NSAID and Coxib medicine items from term 4 (NSAID= 3.44 %, Coxib= 1.21 %) to term 9 (NSAID= 2.88 %, Coxib= 1.19 %).

Table 4.7 The prevalence and cost of Coxib medicine items for Medicine claim database M

COST AND PREVALENCE OF COXIB ITEMS FOR MEDICINE CLAIM DATABASE M DURING 2005 TO 2006																
		Total data			NSAID data					Coxib data						
Year	Term	Total number items	Average cost /item	Total Cost of items	Total number of NSAID items	Percentage total number of NSAID medicine items (%)*	Average cost /NSAID item	Total cost of NSAID items	Percentage of total cost of NSAID medicine items (%)*	Total number of Coxib items	Coxib medicine items as percentage of total all medicine items (%)*	Coxib medicine items as percentage of all NSAID medicine items (%)**	Average cost /Coxib item	Total cost of Coxib items	Coxib total cost as percentage of total cost for all medicine items (%)*	Coxib total cost as percentage of NSAID total cost (%)**
2005	4	6005321	97.80 (±178.65)	587305503.00	293202	4.88	68.82 (±73.74)	20179291.69	3.44	37563	0.63	12.81	189.48 (±88.58)	7117503.93	1.21	35.27
	5	7332627	92.13 (±192.92)	675587370.00	327063	4.46	60.83 (±68.39)	19896752.38	2.95	27634	0.38	8.45	208.85 (±80.35)	5771250.00	0.85	29.01
	6	6522645	96.66 (±203.11)	630484048.00	301598	4.62	60.39 (±67.60)	18214368.48	2.89	26067	0.40	8.64	208.57 (±78.58)	5436830.24	0.86	29.85
	Total	19860679	95.33 (±192.21)	1893376921.00	921863	4.64	63.23 (±69.80)	58290412.55	3.08	91264	0.46	9.90	200.80 (±83.89)	18325584.17	0.97	31.44
2006	7	6984380	95.68 (±215.17)	668291742.00	322857	4.62	60.07 (±67.21)	19395803.95	2.90	27102	0.39	8.39	207.40 (±80.07)	5620900.77	0.84	28.98
	8	8048497	91.24 (±219.18)	734323606.00	346050	4.30	57.30 (±66.15)	19827697.63	2.70	32048	0.40	9.26	202.73 (±82.44)	6151341.20	0.84	31.02
	9	6440185	100.05 (±251.03)	644329035.00	285334	4.43	64.94 (±71.24)	18528765.44	2.88	45460	0.71	15.93	206.49 (±83.19)	7639331.89	1.19	41.23
	Total	21473074	95.33 (±227.98)	2046944383.00	954241	4.44	60.52 (±68.13)	57752267.02	2.82	104610	0.49	10.96	205.46 (±81.87)	19411573.86	0.95	33.61

* The number of items and the total cost of items, for both NSAIDs and Coxibs, were calculated as a percentage of the total number of items and total cost of all items, in the medicine claim database.

** The number of Coxib items and the cost of Coxib items, were calculated as a percentage of the total number of NSAID items and the total cost of NSAID items, in the medicine claim database.

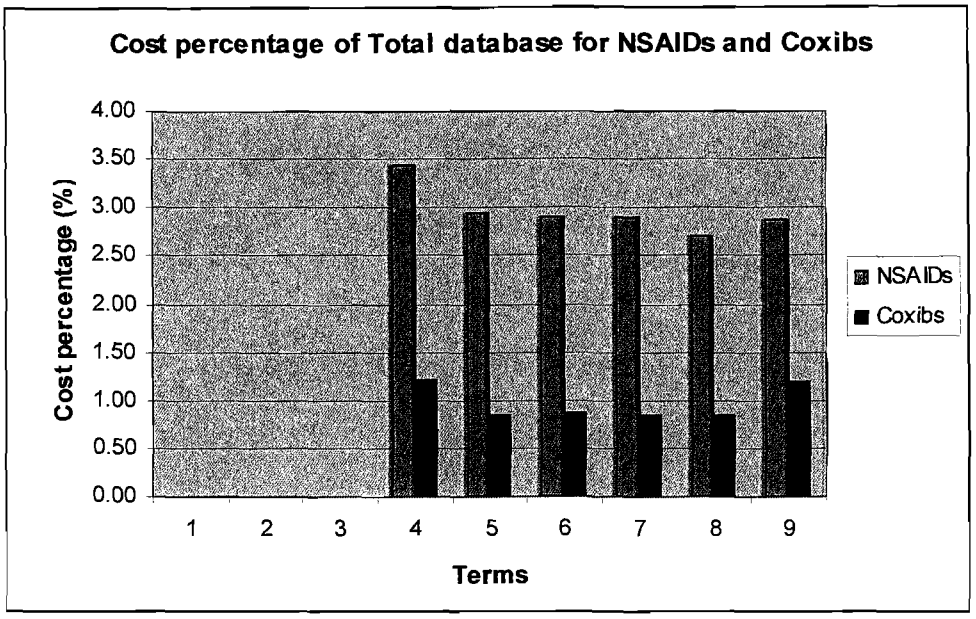

Figure 4.21 The cost percentage of NSAID and Coxib medicine items for Medicine claim database M

Coxib medicine items accounted for almost a third [31.44 %, (R18 325 584.17)] of all NSAID costs in 2005. This number increased to 33.61 % (R19 411 573.86) in 2006, and can be seen in figure 4.21, where the comparative trends of NSAID and Coxib cost percentages over the two-year period are shown.

4.3.2.5 The average number of NSAID prescriptions per patient

According to table 4.8 the average number of general prescriptions remained constant at an average of 7 prescriptions per patient during 2005 (6.98 ±7.83) and 2006 (7.17 ±8.05) respectively. Similarly the average number of NSAID prescriptions per patient also remained constant at an average of approximately 2 prescriptions per patient during 2005 (2.33 ±2.42) and 2006 (2.34 ±2.42) respectively.

Table 4.8 The average number of NSAID prescriptions per patient for Medicine claim database M

Average number of NSAID prescriptions per patient						
Year	**Total number of Rx**	**Average number of Rx/ patient**	**Total number of NSAID Rx's**	**Average number of NSAID Rx /patient**	**Average number of NSAIDs /Rx**	**Total number of NSAID items**
2005	8522574	6.98 (±7.83)	879065	2.33 (±2.42)	1.05 (±0.23)	921863
2006	9046138	7.17 (±8.05)	903983	2.34 (±2.42)	1.06 (±0.24)	954241

Table 4.9 The prevalence of the total number of NSAID prescriptions per patient for medicine claim database M

Prevalence of the total number NSAID prescriptions per patient for Medicine claim database M				
Total number of NSAID Rx's per patient	2005		2006	
	Prevalence (n)	Per cent (%)	Prevalence (n)	Per cent (%)
1	204328	54.22	207789	53.85
2	75538	20.04	77955	20.20
3	35281	9.36	36349	9.42
4	18966	5.03	19586	5.08
5	11138	2.96	11507	2.98
6	7429	1.97	7745	2.01
7	5168	1.37	5295	1.37
8	3624	0.96	3811	0.99
9	2879	0.76	2986	0.77
10	2667	0.71	2729	0.71
11	2769	0.73	2919	0.76
12	3175	0.84	3324	0.86
>12	3909	1.04	3895	1.01

Analysis showed that approximately 26 % of patients received three or more NSAID prescriptions per year for both 2005 and 2006 (table 4.9). Conditions such as rheumatoid arthritis and osteoarthritis are chronic conditions and as chronic conditions should receive six or more prescriptions per year. According to the data in table 4.9 only approximately 8.4 % of patients on medical schemes claimed six or more NSAID prescriptions per year during 2005 and 2006. This might be due to a variety of reasons, including bad patient compliance or limited medical funds. This might be because only rheumatoid arthritis was on the Chronic Disease List and could be claimed as a prescribed minimum benefit (refer to paragraph 2.2.3). It might also be that some of the NSAIDs prescribed were not listed on the medical aid formularies, for example Discovery's chronic illness benefit formulary for 2007 included no Coxibs (Discovery, 2007b:11). These patients could also have paid cash for their chronic prescriptions, or only claimed the prescription two or three times through their medical scheme on acute funds. The different usage categories of acute *vs.* chronic were not further investigated as these aspects are outside the study scope. NSAID patients (n=376 871) represented approximately 30.9 % of all patients (n=1 218 358) on the database in 2005 and approximately 30.6 % of all patients (n=1 259 099) in 2006.

4.3.2.6 The top twenty NSAID products according to prevalence

According to table 4.10 Coxflam® 15mg (sub-pharmacological group 4.1.2) was the NSAID medicine item that was dispensed most often during both 2005 (n=69 317) and 2006 (n=76 120). The average cost per medicine item did not show much change from 2005 with an average of

R74.12, to 2006 with an average of R78.27. The prevalence percentage for Coxflam® was 7.52 % (n=69 317) in 2005 and increased to 7.98 % in 2006.

Table 4.10 The top 20 NSAID products according to prevalence for Medicine claim database M

TOP 20 NSAIDs ACCORDING TO PREVALENCE FOR 2005 AND 2006							
2005							
Number	**Trade name**	**Prevalence (n)**	**Average cost per medicine item (R)**	**Total cost per medicine item (R)**	**Percentage of total prevalence (%)**	**Cost percent-age (%)**	**Cost prevalence index ***
1	Coxflam® 15mg	69317	74.42 (±29.20)	5158351.33	7.52	8.85	1.18
2	Celebrex® 200mg	67993	223.31 (±72.19)	15183633.29	7.38	26.05	3.53
3	Cataflam® D 50mg	66877	83.65 (±35.33)	5594482.98	7.25	9.60	1.32
4	Coxflam® 7.5mg	52745	36.63 (±13.65)	1932241.28	5.72	3.31	0.58
5	Voltaren® 75mg/3ml inj	34292	10.33 (±7.87)	354277.72	3.72	0.61	0.16
6	Adco-diclofenac® 50mg	25358	9.77 (±5.57)	247665.87	2.75	0.42	0.15
7	Inza® 400mg	21225	17.80 (±12.55)	377911.09	2.30	0.65	0.28
8	Adco-diclofenac® 75mg/3ml inj	20221	3.72 (±4.56)	75271.30	2.19	0.13	0.06
9	Panamor® AT 50mg	19882	12.11 (±8.48)	240794.38	2.16	0.41	0.19
10	Pyrocaps® 20mg	17275	17.96 (±6.53)	310193.13	1.87	0.53	0.28
11	Brufen® 400mg	15100	25.07 (±11.21)	378507.95	1.64	0.65	0.40
12	Loxiflam® 15mg	14728	82.90 (±25.04)	1220946.14	1.60	2.09	1.31
13	Loxiflam® 7.5mg	14031	41.06 (±15.43)	576094.10	1.52	0.99	0.65
14	Arthrotec®	13829	134.40 (±58.37)	1858582.08	1.50	3.19	2.13
15	Arthrotec® 75mg	13756	133.02 (±56.39)	1829860.35	1.49	3.14	2.10
16	Sandoz diclofenac® 100SR	13386	50.72 (±13.75)	678922.08	1.45	1.16	0.80
17	Sandoz diclofenac® 50mg tab	12576	12.90 (±7.58)	162294.09	1.36	0.28	0.20
18	Veltex® 75mg	12274	72.76 (±40.92)	893036.99	1.33	1.53	1.15
19	Diclohexal® 50mg	12245	13.88 (±6.96)	170030.15	1.33	0.29	0.22
20	Brexecam® 20mg	11485	68.81 (±29.14)	790334.87	1.25	1.36	1.09
2006							
Number	**Trade name**	**Prevalence (n)**	**Average cost per medicine item (R)**	**Total cost per medicine item (R)**	**Percentage of total prevalence (%)**	**Cost percent-age (%)**	**Cost prevalence index**
1	Coxflam® 15mg	76120	78.27 (±28.40)	5957966.55	7.98	10.32	1.29
2	Celebrex® 200mg	64298	220.61 (±74.82)	14185040.79	6.74	24.56	3.65
3	Cataflam® D 50mg	50426	66.40 (±31.34)	3348145.62	5.28	5.80	1.10
4	Coxflam® 7.5mg	48907	36.83 (±14.47)	1801148.92	5.13	3.12	0.61
5	Dicloflam® blackcurrent	42248	52.57 (±23.81)	2221072.71	4.43	3.85	0.87
6	Voltaren® 75mg/3ml inj	34196	9.59 (±7.72)	328115.21	3.58	0.57	0.16
7	Adco-diclofenac® 50mg	22368	9.23 (±5.92)	206480.40	2.34	0.36	0.15
8	Adco-diclofenac® 75mg/3ml inj	22250	3.00 (±3.99)	66862.52	2.33	0.12	0.05
9	Pyrocaps® 20mg	19171	18.07 (±6.02)	346382.84	2.01	0.60	0.30
10	Inza® 400mg tab	17117	17.47 (±13.58)	299113.32	1.79	0.52	0.29
11	Brufen® 400mg	16664	24.27 (±12.64)	404425.58	1.75	0.70	0.40
12	Panamor® AT 50mg tab	16168	11.35 (±7.66)	183448.44	1.69	0.32	0.19
13	Prexige® 400mg tab	15371	82.38 (±45.66)	1266206.44	1.61	2.19	1.36
14	Merck-diclof® 50mg tab	15333	6.30 (±5.67)	96572.93	1.61	0.17	0.10
15	Loxiflam® 15mg	15241	80.51 (±25.78)	1227084.10	1.60	2.12	1.33
16	Arthrotec® 75mg	13514	133.64 (±57.09)	1806040.73	1.42	3.13	2.21
17	Veltex® 75mg	13431	73.36 (±41.75)	985319.94	1.41	1.71	1.21
18	Sandoz diclofenac® 100SR	12828	50.77 (±14.01)	651222.88	1.34	1.13	0.84
19	Arthrotec® tab	12418	135.10 (±58.95)	1677700.18	1.30	2.90	2.23
20	Sandoz diclofenac® 50mg tab	11910	13.92 (±10.17)	165802.14	1.25	0.29	0.23

* Refer to paragraph 3.5.2.3

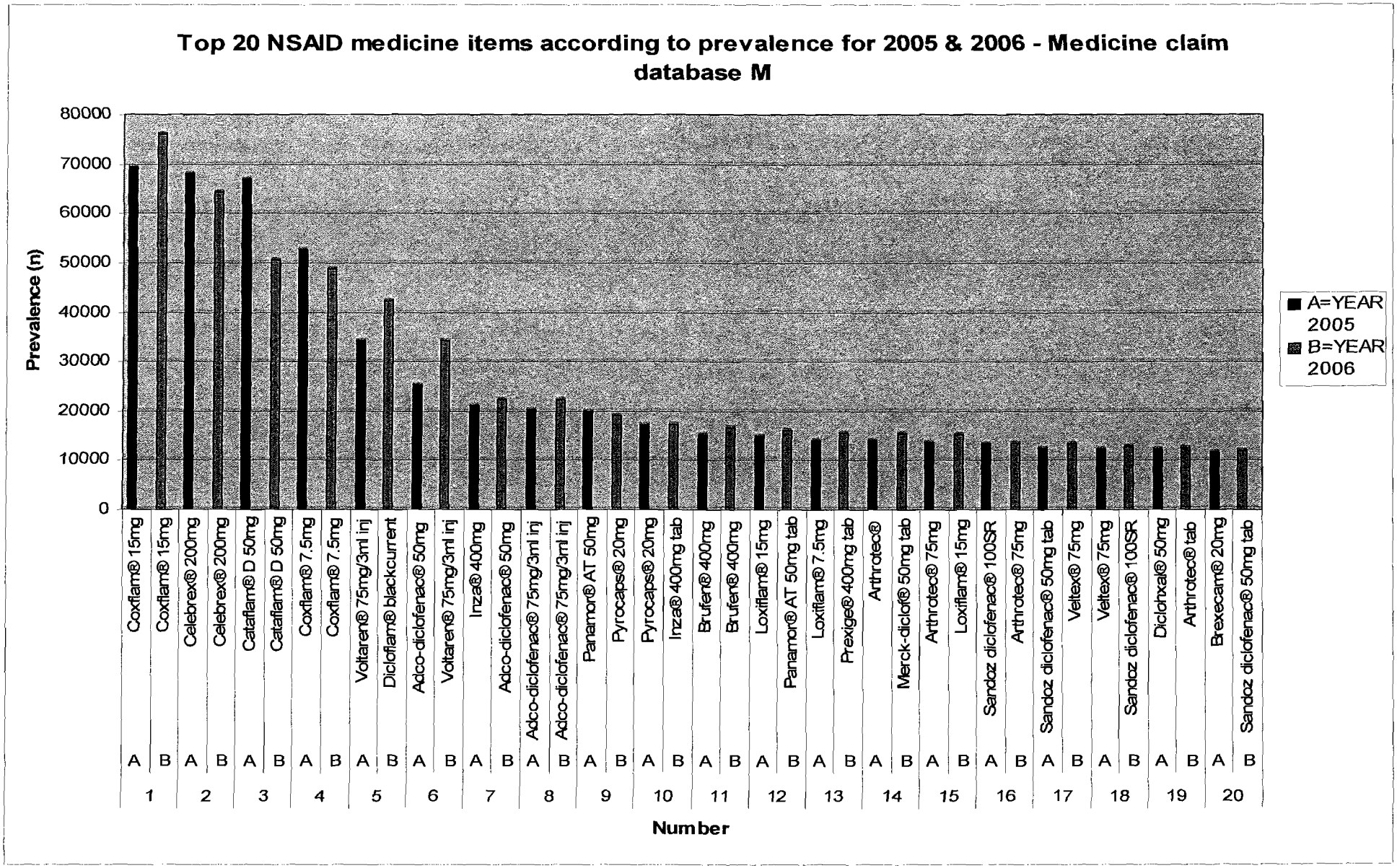

Figure 4.22 The top twenty NSAID medicine items according to prevalence for 2005 and 2006 for Medicine claim database M

The top four NSAID medicine items according to prevalence were Coxflam® 15mg, Celebrex® 200mg, Cataflam® D 50mg and Coxflam® 7.5mg, and remained the same for both 2005 and 2006. Medicine items such as Voltaren® 75mg/3ml injection, Inza® 400mg, Panamor® AT 50mg, Loxiflam® 15mg and Arthrotec® moved down on the top twenty list from 2005 to 2006 while medicine items such as Dicloflam® blackcurrent, Merck-diclofenac® 50mg tablets and the then new drug Prexige® 400mg (refer to paragraph 2.1.6.4) tablets moved up on the top twenty list of medicine items according to prevalence (table 4.10). Prexige® 400mg tablets were dispensed 15 371 times at an average cost of R82.38 (±45.66) and had a total cost of R1 266 206.44 in 2006. The changes on the top twenty medicine item list according to prevalence is illustrated in figure 4.22.

4.3.2.7 The top twenty NSAID products according to cost

According to table 4.11 there are four Coxib medicine items (Celebrex® 200mg, Prexige® 100mg, Celebrex® 100mg and Prexige® 400mg) among the top ten NSAID medicine items according to cost. The top medicine item according to cost (table 4.12) for 2005 and 2006 was Celebrex® 200mg with a total cost of R15 183 633 and R14 185 040 in 2005 and 2006 respectively. Celebrex® 100mg presented with a total cost of R1 572 572 and R1 560 625 in 2005 and 2006 respectively. In 2006, the total cost added up to R2 219 893 and R1 266 206 for Prexige® 100mg and Prexige® 200mg respectively. However, in 2006 only Celebrex® 200mg and Prexige® 400mg appeared on the top twenty list of NSAIDs according to prevalence. This difference in cost and prevalence is also shown in the cost prevalence index (CPI). Celebrex® 200mg was also ranked fourth (Appendix B, table B.2.2) on the list of the top twenty medicine items (all medicine items) according to cost for 2005 and was eighth (Appendix B, table B.2.3) on the same list in 2006.

A CPI higher than one indicates that the therapy utilised is relatively expensive (Refer to paragraph 3.5.2.3). The cost index of Celebrex® 200mg was 3.53 in 2005 and it increased to 3.65 in 2006. Similar results are found for Celebrex® 100mg with a CPI of 2.47 in both 2005 and 2006. In 2006 Prexige® 100mg had a CPI of 3.13 and Prexige® 400mg had a CPI of 1.36. During the study period only five medicine items on the top twenty list of NSAIDs according to cost had a CPI lower than one, these were Coxflam® 7.5mg and Sandoz diclofenac® 100 SR in 2005, and Dicloflam® blackcurrent, Coxflam® 7.5mg and Sandoz diclofenac® 100 SR in 2006.

Table 4.11 indicates that the majority of medicine items among the top twenty NSAIDs according to cost list are relatively expensive according to their CPI.

Table 4.11 The top 20 NSAID products according to cost for Medicine claim database M

TOP 20 NSAIDs ACCORDING TO COST 2005 & 2006							
2005							
Number	**Trade name**	**Prevalence (n)**	**Average cost per medicine item (R)**	**Total cost per medicine item (R)**	**Percentage of total prevalence (%)**	**Cost percent-age (%)**	**Cost prevalence index ***
1	Celebrex® 200mg	67993	223.31 (±72.19)	15183633.29	7.38	26.05	3.53
2	Cataflam® D 50mg	66877	83.65 (±35.33)	5594482.98	7.25	9.60	1.32
3	Coxflam® 15mg	69317	74.42 (±29.20)	5158351.33	7.52	8.85	1.18
4	Coxflam® 7.5mg	52745	36.63 (±13.65)	1932241.28	5.72	3.31	0.58
5	Arthrotec®	13829	134.40 (±58.37)	1858582.08	1.50	3.19	2.13
6	Arthrotec® 75mg	13756	133.02 (±56.39)	1829860.35	1.49	3.14	2.10
7	Celebrex® 100mg	10060	156.32 (±70.23)	1572572.00	1.09	2.70	2.47
8	Bextra® 40mg	11316	126.92 (±87.12)	1436190.21	1.23	2.46	2.01
9	Loxiflam® 15mg	14728	82.90 (±25.04)	1220946.14	1.60	2.09	1.31
10	Xefo® 8mg	11404	91.27 (±49.05)	1040876.44	1.24	1.79	1.44
11	Veltex® 100mg cap	6633	144.61 (±57.01)	959178.98	0.72	1.65	2.29
12	Veltex® 75mg	12274	72.76 (±40.92)	893036.99	1.33	1.53	1.15
13	Synflex® 275mg tab	6485	125.41 (±45.61)	813281.29	0.70	1.40	1.98
14	Brexecam® 20mg tab	11485	68.81 (±29.14)	790334.87	1.25	1.36	1.09
15	Arthrexin® 100mg supp	8347	85.30 (±52.27)	712017.69	0.91	1.22	1.35
16	Nafasol® EC 500mg	6587	107.61 (±57.05)	708813.34	0.71	1.22	1.70
17	Sandoz diclofenac® 100SR	13386	50.72 (±13.75)	678922.08	1.45	1.16	0.80
18	Panamor® SR 100mg tab	8413	74.48 (±20.91)	629939.35	0.91	1.08	1.18
19	Voltaren® 100mg sup	6946	89.90 (±62.15)	624428.67	0.75	1.07	1.42
20	Fortfen® SR 100mg cap	8795	66.70 (±20.54)	586637.96	0.95	1.01	1.05
2006							
Number	**Trade name**	**Prevalence (n)**	**Average cost per medicine item (R)**	**Total cost per medicine item (R)**	**Percentage of total prevalence (%)**	**Cost percent-age (%)**	**Cost prevalenc e index**
1	Celebrex® 200mg	64298	220.61 (±74.82)	14185040.79	6.74	24.56	3.65
2	Coxflam® 15mg	76120	78.27 (±28.40)	5957966.55	7.98	10.32	1.29
3	Cataflam® D 50mg	50426	66.40 (±31.34)	3348145.62	5.28	5.80	1.10
4	Dicloflam® blackcurrent	42248	52.57 (±23.81)	2221072.71	4.43	3.85	0.87
5	Prexige® 100mg tab	11729	189.26 (±65.71)	2219893.34	1.23	3.84	3.13
6	Arthrotec® 75mg	13514	133.64 (±57.09)	1806040.73	1.42	3.13	2.21
7	Coxflam® 7.5mg	48907	36.83 (±14.47)	1801148.92	5.13	3.12	0.61
8	Arthrotec®	12418	135.10 (±58.95)	1677700.18	1.30	2.90	2.23
9	Celebrex® 100mg	10430	149.63 (±69.99)	1560625.85	1.09	2.70	2.47
10	Prexige® 400mg tab	15371	82.38 (±45.66)	1266206.44	1.61	2.19	1.36
11	Loxiflam® 15mg	15241	82.38 (±45.66)	1227084.10	1.60	2.12	1.33
12	Veltex® 75mg	13431	73.36 (±41.75)	985319.94	1.41	1.71	1.21
13	Xefo® 8mg	10065	90.92 (±49.07)	915194.23	1.05	1.58	1.50
14	Veltex® 100mg cap	6123	143.51 (±56.50)	878730.83	0.64	1.52	2.37
15	Brexecam® 20mg tab	11158	67.60 (±30.55)	754343.26	1.17	1.31	1.12
16	Arthrexin® 100mg supp	8824	83.18 (±52.35)	733946.04	0.92	1.27	1.37
17	Sandoz diclofenac® 100SR	12828	50.77 (±14.01)	651222.88	1.34	1.13	0.84
18	Panamor® SR 100mg tab	8341	73.62 (±22.14)	614067.43	0.87	1.06	1.22
19	Synflex® 275mg tab	5129	118.75 (±45.92)	609053.11	0.54	1.05	1.96
20	Nafasol® EC 500mg	5357	110.57 (±58.69)	592317.96	0.56	1.03	1.83

* Refer to paragraph 3.5.2.3

Despite the cost of certain NSAIDs, such as Coxibs, these drugs are widely used for diseases such as rheumatoid arthritis (refer to paragraph 2.1.2.2) and osteoarthritis (refer to paragraph 2.1.2.1) accounting for approximately 4.5 % of all medicine items dispensed (refer to table 4.4).

4.3.2.8 The top twenty NSAID products according to gender

According to table 4.13 the top NSAID medicine item dispensed to females during 2005 was Celebrex® 200mg (n=47 911) with a CPI of 3.32, compared to the male population where the NSAID medicine item dispensed most frequently was Cataflam® D 50mg tablets (n=31 057) with a CPI of 1.49. Among the male population Celebrex® was the third most dispensed item.

Medicine items such as Loxiflam® 15mg, Loxiflam® 7.5mg, Arthrotec® 75mg, Celebrex® 100mg, Brexecam® 20mg and Xefo® 8mg are found on the top twenty list of medicine items dispensed during 2005 for females, but are not on the equivalent list for males for the same period. However, thirteen of the twenty medicine items on the top twenty list for males are items containing diclofenac as active ingredient compared to the eight medicine items containing diclofenac on the equivalent female list. Thompson *et al.* (2005:1309) found that more patients with inflammatory conditions were prescribed COX-2 selective drugs, while more patients with other conditions (mostly non-rheumatological, such as dysmenorrhoea) were prescribed general NSAIDs. This correlates with data from the CDC (2007) and Rizzo (2005:1418), that state that inflammatory conditions like osteoarthritis (refer to paragraph 2.1.2.1.3) and rheumatoid arthritis (refer to paragraph 2.1.2.2.2) are more common among females than males. These conditions are chronic and would require more than one prescription per year. According to table 4.9 approximately 54 % of all NSAID patients received only one NSAID prescription per year during the study period. During the study period (2005 and 2006) Celebrex® (a Coxib) was prescribed more than twice as frequent to females as males. This can in part be explained by the greater frequency of inflammatory conditions in females.

Table 4.12 The total prevalence and cost of NSAIDs according to gender for 2005 and 2006

Year	Gender	Prevalence (n)	Prevalence* (%)	Average cost per NSAID medicine item (R)	Total cost (R)	Total Cost* (%)	Cost prevalence index
2005	Female	562 754	61.04	71.20 (±77.66)	38 247 212.22	65.61	1.07
	Male	358 309	38.87	58.63 (±67.77)	19 999 514.62	34.31	0.88
2006	Female	584 331	61.23	65.51 (±70.80)	38 280 105.76	66.28	1.08
	Male	369 435	38.71	52.63 (±62.88)	19 444 141.05	33.67	0.87

* The prevalence- and cost percentage for the male and female groups do not accumulate to 100 due to the unknown gender group.

Table 4.13 The top 20 NSAIDs according to gender for Medicine claim database M for 2005

Top 20 NSAIDs for 2005 according to Prevalence and Gender							
Female							
Number	**Trade name**	**Prevalence (n)**	**Average cost per NSAID medicine item (R)**	**Total cost (R)**	**Prevalence percent-age (%)**	**Cost percent-age (%)**	**Cost prevalence index ***
1	Celebrex® 200mg cap	47911	223.31 (±72.19	10797181.22	8.51	28.23	3.32
2	Coxflam® 15mg	47064	74.42 (±29.20)	3591398.46	8.36	9.39	1.12
3	Coxflam® 7.5mg	38567	36.63 (±13.65)	1426025.60	6.85	3.73	0.54
4	Cataflam D® 50mg disp tab	35767	83.65 (±35.33)	3001387.89	6.36	7.85	1.23
5	Voltaren® 75mg/3ml inj	18043	10.33 (±7.87)	185550.30	3.21	0.49	0.15
6	Adco-diclofenac® 50mg tab	13809	9.77 (±5.57)	135627.17	2.45	0.35	0.14
7	Inza® 400mg tab	12511	17.80 (±12.55)	231452.15	2.22	0.61	0.27
8	Adco-diclofenac® 75mg/3ml	10488	3.72 (±4.56)	37700.94	1.86	0.10	0.05
9	Loxiflam® 15mg	10440	82.90 (±25.04)	883464.39	1.86	2.31	1.25
10	Pyrocaps® 20mg cap	10335	17.96 (±6.53	188152.04	1.84	0.49	0.27
11	Panamor AT 50mg	10236	12.11 (±8.48)	126432.81	1.82	0.33	0.18
12	Loxiflam® 7.5mg	10072	41.06 (±15.43)	416144.10	1.79	1.09	0.61
13	Arthrotec® tab	9546	134.40 (±58.37)	1321203.39	1.70	3.45	2.04
14	Brufen® 400mg tab	8908	25.07 (±11.21)	224187.83	1.58	0.59	0.37
15	Arthrotec® 75mg tab	8658	133.02 (±56.39)	1164254.01	1.54	3.04	1.98
16	Celebrex® 100mg cap	7574	156.32 (±70.23)	1204212.16	1.35	3.15	2.34
17	Sandoz Diclofenac® 100SR	7342	50.72 (±13.75)	375106.51	1.30	0.98	0.75
18	Brexecam® 20mg tab	7329	68.81 (±29.14)	510424.65	1.30	1.33	1.02
19	Xefo® 8mg	7286	91.27 (±49.05)	673656.11	1.29	1.76	1.36
20	Veltex® 75mg cap	7187	72.76 (±40.92)	535872.52	1.28	1.40	1.10
Male							
Number	**Trade name**	**Prevalence (n)**	**Average cost per NSAID medicine item (R)**	**Total cost (R)**	**Prevalence percent-age (%)**	**Cost percent-age (%)**	**Cost prevalence index**
1	Cataflam D® 50mg disp tab	31057	83.65 (±35.33)	2589217.81	8.67	12.95	1.49
2	Coxflam® 15mg	22203	74.42 (±29.20)	1563489.50	6.20	7.82	1.26
3	Celebrex® 200mg cap	20034	223.31 (±72.19)	4376265.87	5.59	21.88	3.91
4	Voltaren® 75mg/3ml inj	16241	10.33 (±7.87)	168656.62	4.53	0.84	0.19
5	Coxflam® 7.5mg	14162	36.63 (±13.65)	505725.35	3.95	2.53	0.64
6	Adco-diclofenac® 50mg tab	11518	9.77 (±5.57)	111729.19	3.21	0.56	0.17
7	Adco-diclofenac® 75mg/3ml	9731	3.72 (±4.56)	37565.98	2.72	0.19	0.07
8	Panamor AT 50mg	9637	12.11 (±8.48)	114282.54	2.69	0.57	0.21
9	Inza® 400mg tab	8643	17.80 (±12.55)	145184.91	2.41	0.73	0.30
10	Pyrocaps® 20mg cap	6931	17.96 (±6.53)	121887.97	1.93	0.61	0.32
11	Brufen® 400mg tab	6176	25.07 (±11.21)	153902.45	1.72	0.77	0.45
12	Sandoz Diclofenac® 100SR	6022	50.72 (±13.75)	302809.47	1.68	1.51	0.90
13	Sandoz Diclofenac® 50mg tab	5788	12.90 (±7.58)	73771.63	1.62	0.37	0.23
14	Diclohexal® 50mg	5503	13.88 (±6.96)	76838.02	1.54	0.38	0.25
15	Merck-diclof® 50mg tab	5210	6.57 (±4.81)	33367.50	1.45	0.17	0.11
16	Veltex® 75mg cap	5082	72.76 (±40.92)	356917.08	1.42	1.78	1.26
17	Arthrotec® 75mg tab	5073	133.02 (±56.39)	661920.12	1.42	3.31	2.34
18	Dicloflam® blackcurrent	4526	53.82 (±22.28)	245076.33	1.26	1.23	0.97
19	Voltaren® GT 50mg tbec	4367	45.10 (±23.30)	196549.89	1.22	0.98	0.81
20	Arthrotec® tab	4276	134.40 (±58.37)	536543.26	1.19	2.68	2.25

* Refer to paragraph 3.5.2.3

Table 4.14 The top 20 NSAIDs according to gender for Medicine claim database M for 2006

Top 20 NSAIDs for 2006 according to Prevalence and Gender							
Female							
Number	**Trade name**	**Prevalence (n)**	**Average cost per NSAID medicine item (R)**	**Total cost (R)**	**Prevalence percent-age (%)**	**Cost percent-age (%)**	**Cost prevalence index ***
1	Coxflam® 15mg	52788	78.27 (±28.40)	4210829.39	9.03	11.00	1.22
2	Celebrex® 200mg cap	45593	220.61 (±74.82)	10129318.57	7.80	26.46	3.39
3	Coxflam® 7.5mg	36219	36.83 (±14.47)	1348099.88	6.20	3.52	0.57
4	Cataflam D® 50mg disp tab	27135	66.40 (±31.34)	1808026.29	4.64	4.72	1.02
5	Dicloflam® blackcurrent	23458	52.57 (±23.81)	1234279.45	4.01	3.22	0.80
6	Voltaren® 75mg/3ml inj	18247	9.59 (±7.72)	176007.83	3.12	0.46	0.15
7	Adco-diclofenac® 50mg tab	11992	9.23 (±5.92)	112319.05	2.05	0.29	0.14
8	Adco-diclofenac® 75mg/3ml	11510	3.00 (±3.99)	34397.66	1.97	0.09	0.05
9	Pyrocaps® 20mg cap	11418	18.07 (±6.02)	208645.63	1.95	0.55	0.28
10	Loxiflam® 15mg	10670	80.51 (±25.78)	876320.15	1.83	2.29	1.25
11	Inza® 400mg tab	10066	17.47 (±13.58)	182579.87	1.72	0.48	0.28
12	Brufen® 400mg tab	9761	24.27 (±12.64)	236945.36	1.67	0.62	0.37
13	Prexige® 400mg tab	9669	82.38 (±45.66)	799994.78	1.65	2.09	1.26
14	Arthrotec® 75mg tab	8678	133.64 (±57.09)	1173034.19	1.49	3.06	2.06
15	Arthrotec® tab	8563	135.10 (±58.95)	1186628.19	1.47	3.10	2.12
16	Merck-diclof® 50mg tab	8363	6.30 (±5.67)	53405.46	1.43	0.14	0.10
17	Prexige® 100mg tab	8363	189.26 (±65.71)	1592949.65	1.43	4.16	2.91
18	Panamor AT 50mg	8277	11.35 (±7.66)	97278.39	1.42	0.25	0.18
19	Loxiflam® 7.5mg	8113	38.67 (±15.41)	317569.37	1.39	0.83	0.60
20	Celebrex® 100mg cap	7819	149.63 (±69.99)	1182842.99	1.34	3.09	2.31
Male							
Number	**Trade name**	**Prevalence (n)**	**Average cost per NSAID medicine item (R)**	**Total cost (R)**	**Prevalence percent-age (%)**	**Cost percent-age (%)**	**Cost prevalence index**
1	Coxflam® 15mg	23306	78.27 (±28.40)	1745441.65	6.31	8.98	1.42
2	Cataflam D® 50mg disp tab	23269	66.40 (±31.34)	1538693.23	6.30	7.91	1.26
3	Dicloflam® blackcurrent	18776	52.57 (±23.81)	986044.75	5.08	5.07	1.00
4	Celebrex® 200mg cap	18664	220.61 (±74.82)	4045837.21	5.05	20.81	4.12
5	Voltaren® 75mg/3ml inj	15944	9.59 (±7.72)	152073.23	4.32	0.78	0.18
6	Coxflam® 7.5mg	12666	36.83 (±14.47)	452205.84	3.43	2.33	0.68
7	Adco-diclofenac® 75mg/3ml	10740	3.00 (±3.99)	32464.86	2.91	0.17	0.06
8	Adco-diclofenac® 50mg tab	10361	9.23 (±5.92)	93967.61	2.80	0.48	0.17
9	Panamor AT 50mg	7886	11.35 (±7.66)	86131.12	2.13	0.44	0.21
10	Pyrocaps® 20mg cap	7751	18.07 (±6.02)	137705.69	2.10	0.71	0.34
11	Inza® 400mg tab	7008	17.47 (±13.58)	115589.64	1.90	0.59	0.31
12	Merck-diclof® 50mg tab	6958	6.30 (±5.67)	43061.69	1.88	0.22	0.12
13	Brufen® 400mg tab	6897	24.27 (±12.64)	167310.37	1.87	0.86	0.46
14	Prexige® 400mg tab	5695	82.38 (±45.66)	465617.60	1.54	2.39	1.55
15	Veltex® 75mg cap	5659	73.36 (±41.75)	399813.53	1.53	2.06	1.34
16	Sandoz Diclofenac® 100SR	5612	50.77 (±14.01)	284662.12	1.52	1.46	0.96
17	Sandoz Diclofenac® 50mg tab	5352	13.92 (±10.17)	72265.43	1.45	0.37	0.26
18	Diclohexal® 50mg	4855	13.49 (±7.58)	66347.63	1.31	0.34	0.26
19	Arthrotec® 75mg tab	4833	133.64 (±57.09)	632566.01	1.31	3.25	2.49
20	Loxiflam® 15mg	4556	80.51 (±25.78)	349525.57	1.23	1.80	1.46

* Refer to paragraph 3.5.2.3

The total prevalence for all NSAID medicine items (table 4.12) dispensed to females during 2005 was 562 754 NSAID medicine items (61 %) with a total cost of R38 247 212 (65.6 %), compared to a total prevalence of 358 309 NSAID medicine items dispensed to males with a total cost of R19 999 514 during the same period. In 2006 the total prevalence for all NSAID medicine items dispensed to females was 584 331 NSAID medicine items (61.2 %) with a total cost of R38 280 105 (66.3 %), compared to a total prevalence of 369 435 NSAID medicine items (38.7 %) dispensed to males with a total cost of R19 444 141 (33.7 %) during the same period. This indicates that the female population used approximately 22 % more NSAID medicine items than the male population, while accounting for approximately 31 % more of the cost during both 2005 and 2006. This correlates with data from the CDC (Centre for Disease Control) that females are more likely to suffer from osteoarthritis (refer to paragraph 2.1.2.1.3) and that females between the age of 15 and 45 predominate rheumatoid arthritis with a 6:1 ratio and has a peak incidence between the ages of 40 and 60 (refer to paragraph 2.1.2.2.2). The prevalence of each individual medicine item dispensed remains higher for females than males.

In 2005 there was no practical significant difference (d-value 0.16) in average cost per NSAID medicine item (refer to table 4.12) between females (R71.20 ±77.66) and males (R58.63 ±67.77). In 2006 there was also no practical significant difference in average cost per NSAID medicine item between females (R65.51 ±70.80) and males (R52.63 ±62.88), with a d-value of 0.18.

According to table 4.14 the top NSAID medicine item dispensed to both females and males during 2006 was Coxflam® 15mg tablets with a prevalence of n=52 788 in the female population and a prevalence of n=23 306 in the male population. Coxflam® 15mg tablets thus replaced both Celebrex® 200mg among females and Cataflam® D 50mg tablets among males, and became the most frequently prescribed NSAID medicine item among both females and males. In 2006 the prevalence of Celebrex® 200mg (n=45 593) decreased by 2 318 items in comparison with the previous year, and the prevalence of Cataflam® D 50mg (n=23 269) decreased by 7 788 items in comparison with the previous year.

The only Coxib on the top twenty list of NSAID medicine items dispensed to males in 2006 was Celebrex 200mg (n=18 664) in the fourth place. There were, however, four Coxibs on the top twenty list of NSAID medicine items dispensed to females, i.e. Celebrex 200mg (n=45 593), Prexige® 400mg (n=9 669), Prexige® 100mg (n=8 363) and Celebrex® 100mg (n=7 819).

4.3.2.9 The cost and prevalence of NSAID medicine items according to age for medicine claim database M

For the purpose of this study the data from medicine claim database M were divided into five age groups, which are as follows:

Age group 1	0 ≤ 9 years
Age group 2	9 ≤ 19 years
Age group 3	19 ≤ 45 years
Age group 4	45 ≤ 59 years
Age group 5	59 < years

According to table 4.15 age group one (0 ≤ 9 years) had a prevalence of 1.7 % (n=15 886), and accounted for 0.93 % (R546 080.19) of the total cost of all NSAID medicine items in 2005. In 2005 in age group one, sub-pharmacological group 4.1.1 (COX-inhibitors) accounted for 98 % of the prevalence as well as 97 % of the medicine cost. Age group two (9 ≤ 19 years) demonstrated a prevalence of 4.6 % (n=42 414) and accounted for approximately 2.4 % (R=1 422 840.87) of the total cost of all NSAID medicine items in 2005. In age group two, sub-pharmacolgical group 4.1.1 (COX-inhibitors) accounted for approximately 92 % of the prevalence in as well as 85 % of the cost in 2005 while sub-pharmacological groups 4.1.2 and 4.1.3 both accounted for approximately 7 % of the total cost in the same age group. Age group three (19 ≤ 45 years) had the highest prevalence in 2005 with 33.8 % (n=311 800) but only represented approximately 23 % (R13 565 464.96) of the total cost of all NSAIDs for 2005. This might be because sub-pharmacological group 4.1.1 represented 85 % (n=266 338) of the medicine items claimed in this age group with an average cost of R36.77 (±42.92), and accounted for a little over 70 % (R9 794 052.40) of the total cost for this age group during 2005. Age group four (45 ≤ 59 years) had a prevalence of 29.4 % (n=270 988) but represented approximately 27.6 % (R16 119 667.33) of the total cost of all NSAIDs for 2005. Age group four had a lower prevalence than age group three, but represented a greater percentage of the cost, possibly due to sub-pharmacological groups 4.1.2 and 4.1.3 representing 16 % and 8 % of the prevalence respectively, with an average cost per item of R60.67 (±39.28) and R196.26 (±90.70) for 2005. Similarly, age group 5 (59 < years) had a prevalence of 30.4 % (n=280 775), more than three per cent lower than that of age group three but represented approximately twice [45 % (n=R26 636 359.20)] the cost of age group three for 2005. Sub-pharmacological groups 4.1.2 and 4.1.3 represented 30 % and 19 % of the prevalence for this age group and 20 % and 43 % of the cost for this age group respectively. Age group 5 represented almost 46 % of the total cost of all NSAID medicine items for 2005 due to the relatively high prevalence of Coxibs (sub-

pharmacological group 4.1.3) in this age group. Figure 4.23 illustrates the prevalence of NSAID use according to the different age groups for 2005 and 2006.

Table 4.15 The prevalence of different sub-pharmacological groups in different age groups for Medicine claim database M for 2005 to 2006

PREVALENCE OF DIFFERENT AGE GROUPS PER SUB-PHARMACOLOGICAL GROUP FOR DATABASE M 2005-2006								
Year	**Age group**	**Sub-pharmacological group**	**Prevalence (n)**	**Prevalence percentage (%)**	**Average cost (R)**	**Total cost (R)**	**Cost percentage (%)**	**Cost prevalence index ****
2005	**1**	4.1.1	15665	98.61	33.85 (±24.88)	530333.36	97.12	0.98
		4.1.2	171	1.08	48.47 (±36.75)	8288.29	1.52	1.41
		4.1.3	50	0.31	149.17 (±77.64)	7458.54	1.37	4.34
	2	4.1.1	38892	91.70	31.24 (±37.74)	1214896.97	85.39	0.93
		4.1.2	2669	6.29	38.15 (±28.44)	101812.49	7.16	1.14
		4.1.3	853	2.01	124.42 (±78.32)	106131.41	7.46	3.71
	3	4.1.1	266338	85.42	36.77 (±42.92)	9794052.40	72.20	0.85
		4.1.2	31262	10.03	50.12 (±36.23)	1566823.61	11.55	1.15
		4.1.3	14200	4.55	155.25 (±85.14)	2204588.95	16.25	3.57
	4	4.1.1	204051	75.30	44.18 (±50.01)	9015690.59	55.93	0.74
		4.1.2	44497	16.42	60.67 (±39.28)	2699841.39	16.75	1.02
		4.1.3	22440	8.28	196.26 (±90.70)	4404135.35	27.32	3.30
	5	4.1.1	142610	50.79	67.09 (59.66)	9568347.27	35.92	0.71
		4.1.2	84444	30.08	64.71 (±36.63)	5464742.01	20.52	0.68
		4.1.3	53721	19.13	215.99 (±74.95)	11603269.92	43.56	2.28
Total	**Age group 1**		15886	1.72	34.37 (±26.21)	546080.19	0.93	0.54
	Age group 2		42414	4.60	33.55 (±40.65)	1422840.87	2.44	0.53
	Age group 3		311800	33.82	43.51 (±51.45)	13565464.96	23.27	0.69
	Age group 4		270988	29.40	59.48 (±67.40)	16119667.33	27.65	0.94
	Age group 5		280775	30.46	94.87 (±82.21)	26636359.20	45.70	1.50

Table 4.15 (continued)

Year	Age group	Sub-pharmacological group	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percentage (%)	Cost prevalence index **
2006	**1**	4.1.1	15228	98.48	31.66 (±23.84)	482067.63	96.94	0.98
		4.1.2	169	1.09	44.68 (±32.03)	7551.36	1.52	1.39
		4.1.3	66	0.43	115.96 (±80.21)	7653.40	1.54	3.61
	2	4.1.1	39878	91.21	28.50 (±37.43)	1136516.17	83.35	0.91
		4.1.2	2807	6.42	40.11 (±31.16)	112604.64	8.26	1.29
		4.1.3	1038	2.37	110.16 (±74.53)	114345.16	8.39	3.53
	3	4.1.1	266944	84.50	32.44 (±38.43)	8658642.44	68.24	0.81
		4.1.2	31965	10.12	50.47 (±37.73)	1613201.38	12.71	1.26
		4.1.3	17002	5.38	142.12 (±89.58)	2416273.76	19.04	3.54
	4	4.1.1	214898	74.14	39.32 (±46.20)	8450346.41	52.20	0.70
		4.1.2	48127	16.60	61.79 (±37.63)	2973998.03	18.37	1.11
		4.1.3	26819	9.25	177.61 (±92.09)	4763367.84	29.43	3.18
	5	4.1.1	139344	48.17	63.60 (±58.33)	8861725.83	32.80	0.68
		4.1.2	90271	31.20	66.95 (±36.33)	6044039.27	22.37	0.72
		4.1.3	59685	20.63	202.90 (±78.60)	12109933.7	44.83	2.17
Total	**Age group 1**		15463	1.62	32.16 (±25.09)	497272.39	0.86	0.53
	Age group 2		43723	4.58	31.18 (±40.39)	1363465.97	2.36	0.52
	Age group 3		315911	33.11	40.16 (±49.45)	12688117.58	21.97	0.66
	Age group 4		289844	30.37	55.85 (±64.67)	16187712.28	28.03	0.92
	Age group 5		289300	30.32	93.38 (±80.28)	27015698.80	46.78	1.54

* The number of NSAID items per sub-pharmacological group, were calculated as a percentage of the total number of NSAID items per age group, as well as the number of NSAID items per age group as a percentage of the total number of all NSAID items per year.

** Refer to paragraph 3.5.2.3

Age group 1 ($0 \leq 9$ years)
Age group 2 ($9 \leq 19$ years)
Age group 3 ($19 \leq 45$ years)
Age group 4 ($45 \leq 59$ years)
Age group 5 ($59 <$ years)

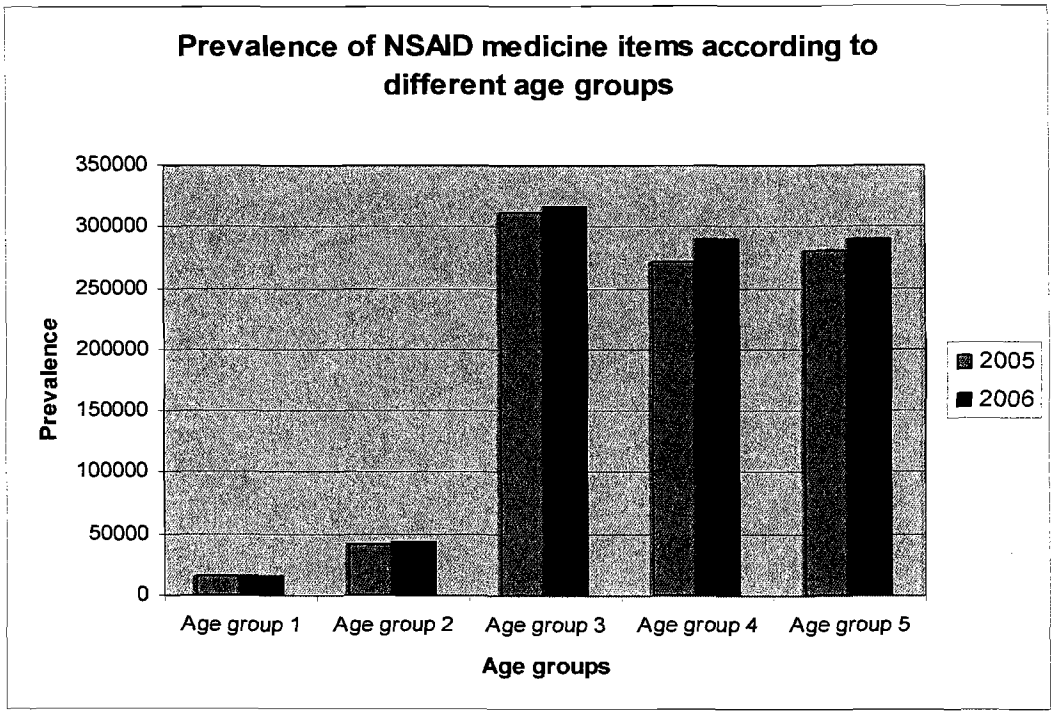

Figure 4.23 The prevalence of NSAID use according to different age groups for 2005 and 2006 for medicine claim database M.

Table 4.15 indicates similar trends for 2005 and 2006, with a prevalence of 1.6 % and 4.6 % for age groups one and two respectively, representing 0.9 % and 2.3 % of the total cost of NSAIDs during 2006. Age group three (19 $\leq$ 45 years) still had the highest prevalence in 2006 with 33.1 % (n=315 911) but only represented approximately 22 % (R12 688 117.58) of the total cost of all NSAIDs for 2006. In age group three sub-pharmacological group 4.1.1 represented 85 % (n=266 944) of the medicine items claimed in this age group and accounted for 68 % (R8 658 642.44) of the total cost for this age group during 2006. Age groups four and five both had a prevalence of approximately 30 % (n=289 844 and n=289 300 respectively) and represented approximately 28 % (R16 187 712.28) and 47 % (R27 015 698.80) of the total cost of all NSAIDs for 2006 respectively. In age group 5 Coxibs represented 21 % of the prevalence, but 45 % of the cost. Figure 4.24 illustrates the total cost of NSAID medicine items according to the different age groups.

The CPI of age groups one to four were all below one for the years 2005 and 2006, and indicate the relative inexpensiveness of NSAID therapy in these age groups. However, age group five had a CPI above one for both years indicating the relative expensiveness of NSAID therapy in this age group, mainly due to the high prevalence of Coxibs in this age group.

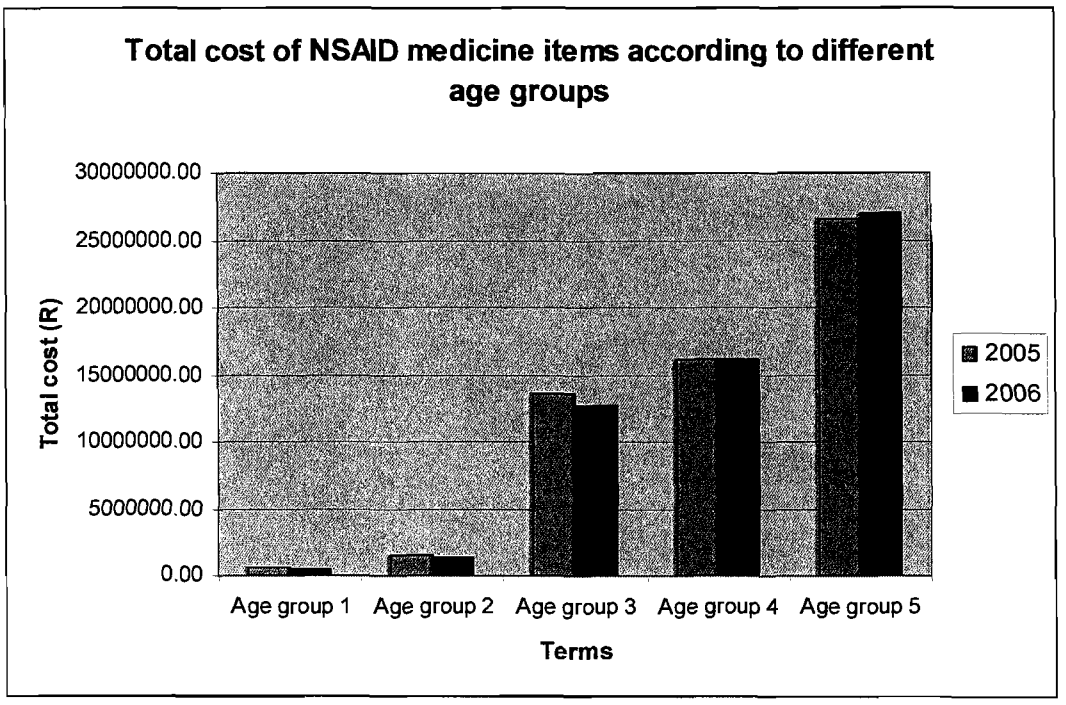

Figure 4.24 The total cost of NSAID use according to different age groups for 2005 and 2006 for medicine claim database M

4.3.2.10 The prevalence of NSAID active ingredients per year for medicine claim database M

According to table 4.16 diclofenac was the active ingredient most prescribed during the study period, with a prevalence percentage of 40.62 % (n=374 439) and 40.76 % (n=388 971) in 2005 and 2006 respectively. This correlates with data from a study by Thompson *et al.* (2005:1309), where they found that diclofenac (38 %) in various forms was the commonest prescribed drug, followed by ibuprofen (24 %) and meloxicam (9 %). The data from medicine claim database M, however, show that meloxicam is the second most prescribed active ingredient with a percentage of 17.69 % (n=163 043) in 2005 and 18.17 % (n=173 339) in 2006, compared to ibuprofen at 10.13 % (n=93 415) in 2005 and 9.98 % (n=95 270) in 2006. The increased use of meloxicam rather than ibuprofen might be due to prescribers' perception of the safety and gastro-intestinal side-effects (refer to paragraph 2.1.5.1) associated with ibuprofen.

The data for NSAID active ingredients for 2005 and 2006 were combined and illustrated in figure 4.25, showing diclofenac with a prevalence of 40 % and celecoxib with a prevalence of 9 % for the study period. The national prescribing centre (NPC, 2007:2) stated that 46 % of all NSAIDs prescribed in England from April to June 2007 contained diclofenac, 25 % ibuprofen, 6.5 % meloxicam, and 3.1 % celecoxib.

Table 4.16 The prevalence of NSAID active ingredients per year for Medicine claim database M

PREVALENCE OF NSAID ACTIVE INGREDIENTS PER YEAR FOR MEDICINE CLAIM DATABASE M								
Year	**Pharm-code**	**Active ingredient**	**Prevalence (n)**	**Prevalence per centage (%)**	**Average cost per medicine item (R)**	**Total cost (R)**	**Cost percentage (%)**	**Cost prevalence index ***
2005	**4.1.1**	Diclofenac	374439	40.62	41.67 (±45.00)	15603569.14	26.77	0.66
		Diclofenac/ misoprostol	27585	2.99	133.71 (±57.39)	3688442.43	6.33	2.11
		Flurbiprofen	2	0.00	89.41 (±22.56)	178.82	0.00	1.41
		Ibuprofen	93415	10.13	22.40 (±32.81)	2092650.32	3.59	0.35
		Indomethacin	36115	3.92	34.69 (±48.69)	1252973.13	2.15	0.55
		Ketoprofen	8671	0.94	82.13 (±32.73)	712165.58	1.22	1.30
		Lornoxicam	16275	1.77	74.09 (±50.59)	1205851.20	2.07	1.17
		Meclofenamic acid	4	0.00	85.35 (±62.62)	341.40	0.00	1.35
		Nabumetone	2025	0.22	100.15 (±45.93)	202801.30	0.35	1.58
		Naproxen	42034	4.56	70.32 (±62.30)	2955874.82	5.07	1.11
		Phenylbutazone	453	0.05	20.84 (±10.86)	9439.04	0.02	0.33
		Piroxicam	63767	6.92	32.96 (±24.75)	2101987.19	3.61	0.52
		Sulindac	983	0.11	134.37 (±52.36)	132089.08	0.23	2.13
		Tenoxicam	1788	0.19	92.26 (±111.36)	164957.14	0.28	1.46
	4.1.2	Meloxicam	163043	17.69	60.36 (±39.68)	9841507.79	16.88	0.95
	4.1.3	Celecoxib	78053	8.47	214.68 (±75.36)	16756205.29	28.75	3.40
		Parecoxib	1874	0.20	69.46 (±43.43)	130166.51	0.22	1.10
		Rofecoxib	21	0.00	143.91 (±130.21)	3022.16	0.01	2.28
		Valdecoxib	11316	1.23	126.92 (±87.12)	1436190.21	2.46	2.01
	Total		921863	100.00	63.23 (±69.80)	58290412.55	100.00	1.00
2006	**4.1.1**	Diclofenac	388971	40.76	37.21 (±40.18)	14472142.41	25.06	0.61
		Diclofenac/ misoprostol	25932	2.72	134.34 (±57.99)	3483740.91	6.03	2.22
		Ibuprofen	95270	9.98	20.36 (±31.39)	1939685.24	3.36	0.34
		Indomethacin	39014	4.09	31.61 (±47.57)	1233439.33	2.14	0.52

Table 4.16 (continue)

Year	Pharm-code	Active ingredient	Prevalence (n)	Prevalence per centage (%)	Average cost per medicine item (R)	Total cost (R)	Cost percentage (%)	Cost prevalence index *
2006	**4.1.1**	Ketoprofen	6289	0.66	82.90 (±35.94)	521359.67	0.90	1.37
		Lornoxicam	13777	1.44	75.55 (±50.94)	1040915.18	1.80	1.25
		Meclofenamic acid	2	0.00	87.39 (±7.56)	174.79	0.00	1.44
		Nabumetone	2555	0.27	100.33 (±54.22)	256356.86	0.44	1.66
		Naproxen	41860	4.39	59.66 (±57.62)	2497560.64	4.32	0.99
		Phenylbutazone	526	0.06	21.80 (±11.16)	11466.83	0.02	0.36
		Piroxicam	59872	6.27	31.72 (±23.94)	1898949.75	3.29	0.52
		Sulindac	460	0.05	135.32 (±54.31)	62246.26	0.11	2.24
		Tenoxicam	1764	0.18	97.09 (±120.06)	171260.61	0.30	1.60
	4.1.2	Meloxicam	173339	18.17	62.02 (±37.49)	10751394.68	18.62	1.02
	4.1.3	Celecoxib	74728	7.83	210.71 (±78.14)	15745666.64	27.26	3.48
		Lumiracoxib	27100	2.84	128.64 (±76.52)	3486099.78	6.04	2.13
		Parecoxib	2774	0.29	64.82 (±46.49)	179807.29	0.31	1.07
		Valdecoxib	8	0.00	0.02 (±0.02)	0.15	0.00	0.00
	Total		954241	100.00	60.52 (±68.13)	57752267.02	100.00	1.00

* Refer to paragraph 3.5.2.3

Products containing diclofenac as active ingredient show an average cost ranging from approximately R3.00 (CPI of 0.05) to R144.00 (CPI of 2.29) according to table C.1.1 (Appendix C). Medicine items such as flurbiprofen, meclofenamic acid, nabumetone, phenylbutazone, sulindac, tenoxicam, parecoxib and rofecoxib were not depicted in figure 4.25 because they had a prevalence percentage lower than 0.5 %.

A cost prevalence index (CPI) higher than one indicated a relatively expensive therapy. In 2005 there were 185 NSAID products prescribed and claimed through Medicine claim database M, 68 of which had a CPI higher than one (Appendix C, table C.1.1). Thus more than one third of all NSAID products prescribed could be considered relatively expensive.

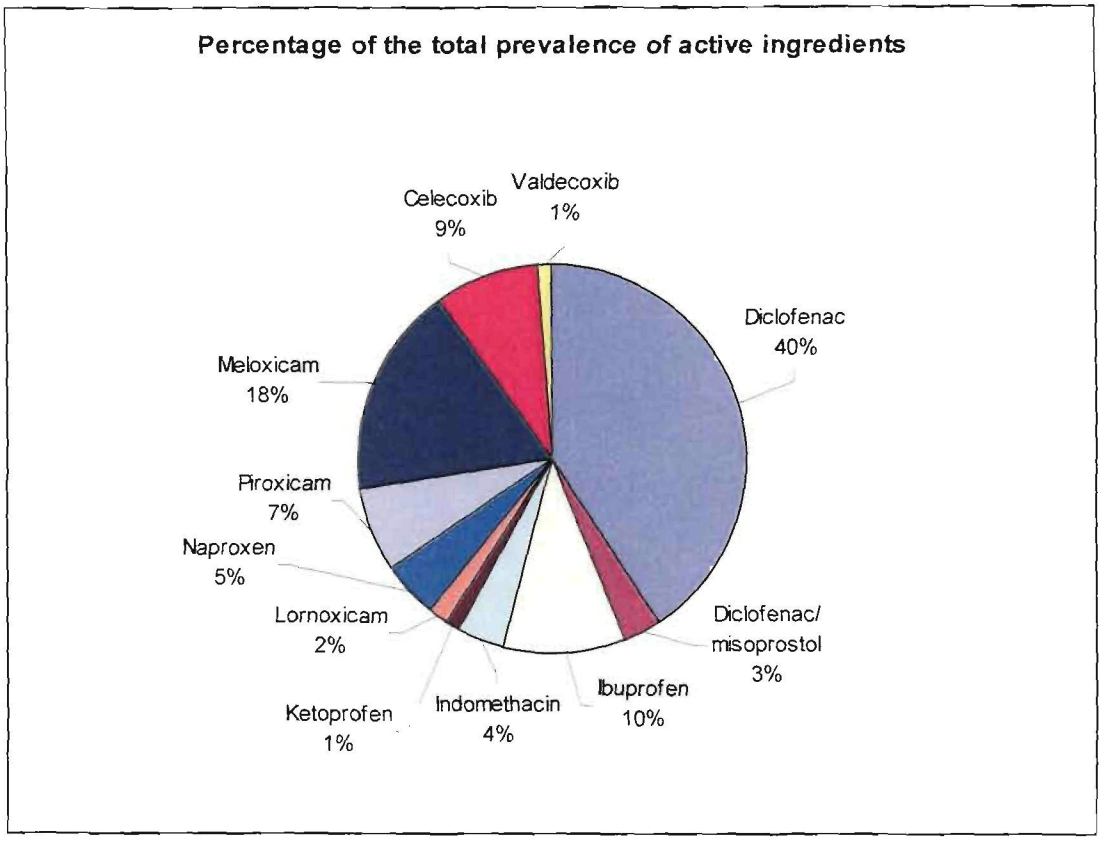

Figure 4.25 The percentage of the total prevalence of NSAID active ingredients for the combined data of 2005 and 2006

These include products such as Adco-sulindac®, Arthrotec®, Bextra®, Brufen® retard, Celebrex®, Feldene®, Indocid® , Inflaban®, Mobic®, Synflex®, Tilcotil®, Veltex®, Vioxx® and Xycam® with CPI counts higher than two, and an average cost per NSAID product of R63.23 (±69.80) per year for 2005 (Appendix C, table C.1.1). Individual products did not show much change from 2005 to 2006, except where drugs were removed or where new drugs were introduced such as Prexige®. The prevalence of Mobic® 15mg decreased from 1 888 medicine items claimed during 2005 to 1 250 medicine items dispensed during 2006, while generics such as Flexocam® 15mg and Flexocam® 7.5mg increased from 1 150 medicine items claimed and 540 medicine items claimed during 2005 to 4 762 medicine items claimed and 2 508 medicine items claimed in 2006 for Flexocam® 15mg and Flexocam® 7.5mg respectively. The average cost per NSAID product per year decreased from R63.23 (±69.80) in 2005 to R60.52 (±68.13) in 2006 (Appendix C, table C.1.1).

4.3.2.11 NSAID medicine usage according to diagnosis code

According to the data from medicine claim database M, shown in table 4.17, approximately 36 % (n=39 213) of all NSAIDs were prescribed for diagnosis M15, which is the ICD-10 code

for arthrosis (WHO, 2007a), including but not limited to osteoarthrosis. Similarly approximately 28 % (n=30 077) of all NSAIDs prescribed in 2006 were for diagnosis M13 (Anon., 2008c), which were for "other" forms of arthritis, not including rheumatoid arthritis, equally diagnosis M19 ("other" arthrosis) and M25 (other joint disorders, not elsewhere classified) were all for some form of arthritis or arthrosis.

Table 4.17 The prevalence and diagnosis code for NSAID medicine items in 2006 for Medicine claim database M

	Diagnosis Code (ICD-10 code)	Prevalence (n)	Percentage (%)
1	M15	39213	36.21
2	M13	30077	27.77
3	Q22	20624	19.04
4	M19	7884	7.28
5	M25	3874	3.58

The CDC stated that one in five (over 21 %) of adults in the United States (refer to paragraph 2.1.2.2.7), according to the National Health Interview Survey (NHIS) reported having doctor diagnosed arthritis during 2003-2005 (CDC, 2006:1089). In the USA the CDC (2007) estimated that 21 million adults have osteoarthritis and 2.1 million adults are affected by rheumatoid arthritis. The CDC also stated that an estimated 5.1 million adults are diagnosed with gout and an estimated 3.7 million adults with fibromyalgia. Three of the five top diagnoses mentioned in table 4.16 were for "other" or "unspecified" forms of inflammatory diseases. This is possibly due to incomplete diagnosis or poor compliance or understanding of the ICD-10 coding system.

4.3.4 Summary for Medicine claim database M

- Approximately 10 % of all prescriptions dispensed through Medicine claim database M during the study period were NSAID prescriptions.
- NSAID medicine items represented an average of 4.5 % of all medicine items during the study period.
- The average cost per medicine item was R95.33 in 2005 and 2006 while the average cost per NSAID medicine item decreased from R66.31 (±74.23) in 2005 to R63.89 (±72.35) in 2006.
- NSAID medicine items represented between 3.1 % and 2.8 % of the cost of all medicine items during the study period.

- In 2005 the prevalence of Coxibs (n=91 264) was approximately 62 per cent lower than that of COX-inhibitors (n=667 556) while the average cost per item for Coxibs (R200.80 ±83.89) was significantly higher (d-value 1.85), than that of COX-inbibitors (R45.12 ±50.03).
- The average cost per Coxib medicine item for Medicine claim database M was 14.2 % lower than that of Medicine claim database I (table 4.3) in 2005, and 19.8 % lower than that of Medicine claim database I (table 4.3) in 2006.
- Coxib medicine items accounted for almost a third [31.44 %, (R18 325 584.17)] of all NSAID costs in 2005. This number increased to 33.61 % (R19 411 573.86) in 2006.
- The CPI for all NSAIDs during 2005 and 2006 is approximately 0.6 for both medicine claim databases, indicating that NSAIDs as a group are relatively inexpensive.
- The CPI for both COX-inhibitors and Selective COX-2 inhibitors was approximately one or below one for both medicine claim databases for both years of the study period, indicating relative inexpensiveness. However, Coxibs according to both databases, had a CPI higher than three for 2005 and 2006, indicating them to be relatively expensive.
- Only approximately 8.4 % of patients on medical schemes claimed six or more NSAID prescriptions per year.
- The top four NSAID medicine items according to prevalence were Coxflam® 15mg, Celebrex® 200mg, Cataflam® D 50mg and Coxflam® 7.5mg, and remained the same for both 2005 and 2006.
- The top medicine item according to cost (table 4.12) for 2005 and 2006 was Celebrex® 200mg with a total cost of R15 183 633 and R14 185 040 in 2005 and 2006 respectively.
- The top NSAID medicine item dispensed to females during 2005 was Celebrex® 200mg (n=47 911) with a CPI of 3.32, compared to the male population where the NSAID medicine item dispensed most was Cataflam® D 50mg tablets (n=31 057) with a CPI of 1.49.
- The total prevalence for all NSAID medicine items dispensed to females during 2005 was 562 754 NSAID medicine items (table 4.12) with a total cost of R38 247 212, compared to a total prevalence of 358 309 NSAID medicine items dispensed to males with a total cost of R19 999 514 during the same period. This indicates that the female population used approximately 22 per cent more NSAID medicine items than the male population, while accounting for approximately 31 per cent more of the cost during both 2005 and 2006.

- The top NSAID medicine item dispensed to both females and males during 2006 was Coxflam® 15mg tablets with a prevalence of n=52 788 in the female population and a prevalence of n=23 306 in the male population.
- Diclofenac was the active ingredient most prescribed during the study period accounting for an average of 40 % of the prevalence of all NSAIDs, followed by meloxicam (18 %) and ibuprofen (10 %).
- Similar trends are indicated (table 4.16) for 2005 and 2006, with a prevalence of 1.6 % and 4.6 % for age groups one and two respectively, representing 0.9 % and 2.3 % of the total cost of NSAIDs during 2006. Age group three (19 $\leq$ 45 years) still had the highest prevalence in 2006 with 33.1 % (n=315 911) but only represented approximately 22 % (R12 688 117.58) of the total cost of all NSAIDs for 2006. Age groups four and five both had a prevalence of approximately 30 % (n=289 844 and n=289 300 respectively) and represented approximately 28 % (R16 187 712.28) and 47 % (R27 015 698.80) of the total cost of all NSAIDs for 2006 respectively. In age group 5 Coxibs represented 21 % of the prevalence, but 45 % of the cost.
- The CPI of age groups one to four were all below one for the years 2005 and 2006, and indicated the relative inexpensiveness of NSAID therapy in these age groups. However, age group five had a CPI above one for both years indicating the relative expensiveness of NSAID therapy in this age group, mainly due to the high prevalence of Coxibs in this age group.

4.4 CHAPTER SUMMARY

In this chapter the prevalence and cost of NSAID medicine items have been investigated and discussed as a group, as well as according to sub-pharmacological groups. The top NSAID products were determined according to prevalence, cost and gender, as well as the influences of age on the prevalence of NSAID medicine use. Conclusions and recommendations based on this empirical study will be discussed in chapter five.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

The conclusions of this study, based on the results of the literature review and empirical investigation, will be presented. This chapter will also focus at some limitations of the study and recommendations made from the study.

5.2 CONCLUSIONS

The specific objectives of this study have been set and will be summarised accordingly. The objectives will be listed under the specific objectives of the literature study and the specific objectives of the empirical study.

Specific objectives of the literature study:

- ***The first specific objective was to conceptualise the usage and side-effects of NSAID use.***

In a literature overview of the usage of NSAIDs, it was found that NSAIDs are among some of the most frequently prescribed drugs in use. In a study performed in South Africa in the year 2000, approximately ten per cent of prescriptions claimed through a medical scheme contained one or more NSAID medicine items (Joubert, 2002:260). Although NSAIDs can be prescribed to a patient of almost any age, these drugs are most commonly prescribed to middle-aged or elderly patients due to the high prevalence of diseases such as rheumatoid-arthritis (refer to paragraph 2.1.2.2.2 and table 2.2) and osteoarthritis (refer to paragraph 2.1.2.1.2 and 2.1.2.1.3) among these patients.

NSAIDs can be used for a variety of conditions including different forms of arthritis, dental and bone pain, dysmenorrhoea, headache, gout, Barter's syndrome, trombo-embolic disorders, and relief of pain and inflammation (refer to paragraph 2.1.3). However, NSAIDs are still associated with a range of gastro-intestinal complications and side-effects. Ulcers of the gastro-intestinal tract, as well as bleeding and perforations of the gastro-intestinal tract remain the most common problems associated with NSAID use (refer to table 2.5).

- ***The second specific objective was to review specific cyclo-oxygenase-2 inhibitor (Coxib) use and aspects associated with the withdrawal of these products from the market.***

Due to the gastro-intestinal side-effects associated with NSAID use, as discussed in the first specific objective, drugs which inhibit COX-2 rather than COX-1, such as selective COX-2 inhibitors and specific COX-2 inhibitors (Coxibs) are considered the drugs of choice when treating the high risk patient (e.g. elderly patients). However, a meta-analysis performed by Spiegel *et al.* (2006:30) reflected the rates of dyspepsia indicating a 12 % relative risk reduction for Coxibs (refer to paragraph 2.1.6.5) compared to NSAIDs, while the rates of dyspepsia had a 66 % relative risk reduction for NSAID plus PPI therapy compared to NSAID therapy only.

Despite the advantages of increased gastro-intestinal safety, Coxibs are still used less frequently than other NSAIDs due to the relative high cost associated with their use, and some possible uncertainty about their safety after the withdrawal of first Vioxx® from the market in 2004, followed by Bextra® in 2005 and Prexige® in 2007. These medicine items were associated with life-threatening side-effects (refer to paragraph 2.1.6.4) such as increased risk for cardio-vascular events such as heart-attack and stroke with the use of Vioxx® and Bextra®, and Prexige® due to serious liver side-effects.

- ***The third specific objective was to conceptualise from the literature what managed health care, drug utilisation, pharmacoeconomics and disease management entail.***

Managed health care is a method implemented to contain health care costs. According to Powell (2000:3), managed care can be defined as a collection of techniques used by or on behalf of purchasers of health care benefits to manage and maintain health care costs by influencing patient care decision making through case-by-case evaluation of the appropriateness of care before its provision (refer to paragraph 2.2.2). Managed health care is an economically driven, ever-changing force that not only aims to control the cost of health care, but also the quality of health care and the access to that care. In the RSA managed health care is mainly implemented in the private health care sector, but the principles have also been extensively used in the past and present in the public health care sector (Serfontein, 2008). An example is the restricted availability of medicine through the medicine code system as well as the essential drug list in the public health care sector of South Africa (Department of Health, 2006).

Drug utilisation review (DUR) aims to improve quality of life (refer to paragraph 2.2.6.2) and patient care (Weber, 1999:2), by enhancing therapeutic outcomes, reducing inappropriate pharmaceutical expenditures, and intervening when inappropriate drug use is detected (Strom

& Kimmel, 2006:474). Drug utilisation studies, according to Gray and Clarke (1995:281), aim to provide principles for decision making in the drug and health chain, and should give special attention to the resulting medical, social and economic consequences. According to Waning and Montagne (2001:162), pharmacists conduct drug utilisation studies, as part of their routine activities, and state that DURs are usually done to monitor prescribing patterns. Waning and Montagne (2001:162) also emphasised that drugs recently approved by the FDA and that have shown serious adverse effects in phase III trials, are normally chosen to be monitored via DURs.

Pharmacoeconomic studies are designed to help determine the actual cost of an intervention when all of its costs and savings are incorporated (refer to paragraph 2.2.4.1), and to help ensure the best use of health care resources (Cantor, 2002:s28). Savings can result from fewer adverse events, fewer surgeries, lower mortality and morbidity, improved efficacy, and fewer disabilities. Health care resources are almost always limited, and it is important to analyse new interventions from the perspective of their cost burden. In recent years pharmacologic interventions have absorbed an increasing percentage of health care dollars.

The concept of disease management according to Faxon *et al.* (2004:2653) addresses the full spectrum of health care and aims to be an integrated system for managing patient health care (improve health rather than simply treat disease). The main indicator of success in disease management should be patient outcomes and quality of care, and not simply the ability to reduce health care expenditures (refer to paragraph 2.2.7). Couch (1997:4) defines it as *a knowledge-based process intended to improve continuously the value of health care delivery from the perspectives of those who receive, purchase, provide, supply, and evaluate it.* According to McDonald *et al.* (2004:72) disease management should be a system of care, with the focus on the patient, by containing costs, improving the health outcome, reducing variations in care and improving the quality in care.

Specific objectives of the empirical study for both databases:

The specific objectives of this study were evaluated by using two different medicine claim databases in a section of the private health care sector. Data were analysed for the period 1 January 2004 to 31 December 2006 for medicine claim database I and from 1 January 2005 to 31 December 2006 for medicine claim database M.

- ***The first specific objective was to investigate the usage patterns of NSAID therapy.***

Between 9 and 10.5 per cent of prescriptions dispensed through both medicine claim database I and medicine claim database M during the study period were NSAID prescriptions, and this information coincides with a study by Joubert (2002:260), where NSAID prescriptions accounted for 10 per cent of all prescriptions claimed for a year (1 July 1999 to 30 June 2000). NSAID medicine items also represented an average of 4.5 per cent of all medicine items claimed from medicine claim database I as well as medicine claim database M during the study period. An average of one NSAID medicine item per prescription was maintained for both databases during the study period.

These findings indicate very little change in NSAID prescription and medicine use from 2000 to 2006, and despite the difference in the total number of prescriptions processed by each medicine claim database, the difference in the percentage of NSAID prescriptions and medicine items claimed by the two databases is almost negligible. The trend of NSAID use of the two databases is thus very similar.

- ***The second specific objective was to analyse and calculate the cost of NSAID therapy.***

The average cost per medicine item for medicine claim database I decreased from R124.62 in 2004 to R112.51 in 2005, and R117.76 in 2006 (refer to paragraph 4.2.2.1) compared to the much lower average cost per medicine item of R95.33 in 2005 and 2006 for medicine claim database M (refer to paragraph 4.3.2.1). The average cost per NSAID medicine items for medicine claim database I also decreased from R108.12 in 2004 to R73.74 in 2005 and R71.73 in 2006, compared to medicine claim database M where the average cost per NSAID medicine item decreased from R66.31 in 2005 to R63.89 in 2006. It is clear that both medicine claim databases show similar trends although the average cost per general medicine item as well as NSAID medicine item, has lower costs on medicine claim database M, than on medicine claim database I.

NSAID medicine items on medicine claim database I represented between 3.9 per cent and 2.9 per cent of the cost of all medicine items during the study period, while only representing between 3.1 per cent and 2.8 per cent of the cost of all medicine items claimed through medicine claim database M during the study period, indicating yet again similar trends in the two medicine claim databases.

- ***The third specific objective was to review the use of Coxibs before and after the discontinuing of Vioxx® (refer to paragraphs 2.1.6.3 and 2.1.6.4) on medicine claim database I.***

The prevalence of Coxibs (sub-pharmacological group 4.1.3) decreased significantly from almost 20 per cent in 2004 to 8.4 per cent in 2005, but showed an increase to 10.9 per cent in 2006. The prevalence of both COX-inhibitors (sub-pharmacological group 4.1.1), and Coxibs (sub-pharmacological group 4.1.3) demonstrated a change in term 3 (1 September 2004 to 31 December 2004) when COX-inhibitors showed an increase in use, while Coxibs showed and almost equal but opposite trend with a decrease in use. This could be related to the perceptions of providers and public of Coxibs and their related safety after the withdrawal of Vioxx® on 30 September 2004 (Merck, 2004) and other Coxibs such as Bextra® in 2005 (FDA, 2005), while in 2006 (Term 8), Prexige® was introduced to the South African market and could be responsible for the sudden increase in Coxib use.

Coxib medicine items demonstrated the greatest change in prevalence of items claimed by decreasing almost fourfold from 2004 to 2006. It is concluded that most patients who stopped using Coxibs after the withdrawal of Vioxx®, were prescribed COX-inhibitors, that are known for their possible gastro-intestinal side-effects (refer to paragraph 2.1.5).

- ***The fourth specific objective was to investigate the usage patterns of Coxib therapy.***

In 2004 Coxibs represented approximately 20 per cent of all NSAID medicine items claimed through medicine claim database I (refer to paragraph 4.2.2.2). This number decreased to 8.4 per cent and approximately 11 per cent in 2005 and 2006 respectively. Medicine claim database M revealed similar results where Coxibs represented 9.9 per cent, and approximately 11 per cent of all NSAID medicine items claimed for 2005 and 2006 respectively. The trends on each of the two medicine claim databases correlate. In 2000 Joubert (2002:166) found that Coxibs represented only 2.4 per cent of NSAID medicine items claimed through a medicine claim database. The low use of Coxibs might be due to Vioxx® only entering the market in 1999 (Merck, 2004).

Coxibs represented less than one per cent of all medicine items claimed through both medicine claim databases from 2004 to 2006.

- ***The fifth specific objective was to analyse and calculate the cost of Coxib therapy.***

The average cost per Coxib medicine item claimed through medicine claim database I was twice that of the average cost per general medicine item, and took a decline in term 3 (1 September 2004 to 31 December 2004), while it peaked again in term 7 (1 January 2006 to 30 April 2006). Coxib medicine items accounted for almost half [44.85 %, (R11 636 571.50)] of all NSAID cost in 2004, which decreased to 26.67 % and 39.22 % in 2005 and 2006 respectively, due to the decrease in the percentage of Coxib prevalence during these years.

The average cost per Coxib medicine item for Medicine claim database M was 14.2 % lower than that of Medicine claim database I (refer to table 4.3) in 2005, and 19.8 % lower than that of Medicine claim database I in 2006. Coxib medicine items accounted for almost a third [31.44 %, (R18 325 584.17)] of all NSAID costs in 2005. This number increased to 33.61 % (R19 411 573.86) in 2006.

- ***The sixth and seventh specific objectives was to investigate the usage patterns, and analyse the cost of NSAID therapy per sub-pharmacological group.***

The analysis of NSAIDs according to sub-pharmacological group indicated that COX-inhibitors (sub-pharmacological group 4.1.1) had the highest prevalence among NSAIDs, representing 67 per cent to 80 per cent of the NSAID medicine use from 2004 to 2006 for medicine claim database I. In 2004 and 2006 Coxibs (sub-pharmacological group 4.1.3) had the second highest prevalence among NSAIDs with a prevalence of approximately 20 per cent and 11 per cent respectively. In 2005 Selective COX-2 inhibitors (sub-pharmacological group 4.1.2) had the second highest prevalence among NSAIDs with a prevalence of 12.5 per cent, while in 2004 and 2006 they had the lowest prevalence among NSAID medicine items for medicine claim database I (refer to paragraph 4.2.2.2).

Analysis of medicine claim database M revealed COX-inhibitors (sub-pharmacological group 4.1.1) to have the highest prevalence among NSAID medicine items (refer to paragraph 4.3.2.2) with a prevalence above 70 per cent for both 2005 and 2006. Selective COX-2 inhibotors (sub-pharmacological group 4.1.2) were second with a prevalence between 17 and 18 per cent, while Coxibs (sub-pharmacological group 4.1.3) had the lowest prevalence among NSAID medicine items with a prevalence between 10 and 11 per cent for 2005 and 2006 respectively. The difference in use between the two databases might be due

to the different medical schemes represented by the medicine claim databases and the drugs listed on their formularies (refer to paragraph 4.3.2.5).

In 2004 the prevalence of Coxibs (n=47 938) claimed through medicine claim database I was three and a half times lower than that of COX-inhibitors (n = 161 306) while the average cost per item was approximately three times higher. The prevalence of both COX-inhibitors (sub-pharmacological group 4.1.1), and Coxibs (sub-pharmacological group 4.1.3) demonstrated a change in term 3 when COX-inhibitors showed an increase in use, while Coxibs showed an almost equal but opposite trend with a decrease in use. The cost percentage for COX-inhibitors demonstrated opposite trends from that of Coxibs with a peak during term 5, while Coxibs demonstrated a dip during the same term. COX-inhibitors and Selective COX-2 inhibitors were relatively inexpensive with a CPI of one or below during the study period (refer to paragraph 4.2.2.2), while Coxibs were relatively expensive with a CPI above one during the study period for medicine claim database I.

In 2005 the prevalence of Coxibs (n=91 264) claimed through medicine claim database M was seven times lower than that of COX-inhibitors (n=667 556) while the average cost per item was approximately four and a half times higher at R200.80 (±83.89) in relation to COX-inbibitors at R45.12 (±50.03). The average cost per Coxib medicine item for medicine claim database M was 14.2 per cent and 19.8 per cent lower than that of Medicine claim database I (refer to paragraph 4.2.2.2) in 2005 and 2006 respectively. The CPI for all NSAIDs during 2005 and 2006 is approximately 0.6 for both medicine claim databases and indicate that NSAIDs as a group are relatively inexpensive. The CPI for both COX-inhibitors and Selective COX-2 inhibitors were approximately one or below one for both medicine claim databases for both 2005 and 2006, indicating relative inexpensiveness. However, Coxibs according to both databases, had a CPI higher than three for 2005 and 2006, indicating them to be relatively expensive.

- ***The eighth specific objective was to identify the top twenty NSAIDs according to prevalence, cost, and gender for Database M.***

Analysis revealed that the top four NSAID medicine items according to prevalence (refer to paragraph 4.3.2.6) were Coxflam® 15mg, Celebrex® 200mg, Cataflam® D 50mg and Coxflam® 7.5mg, and remained the same for both 2005 and 2006. The top medicine item according to cost (refer to paragraph 4.3.2.7) for 2005 and 2006 was Celebrex® 200mg,

representing approximately 26 per cent and 24 per cent of the cost of NSAIDs for 2005 and 2006 respectively, whilst the prevalence percentages for Celebrex® 200mg were 7.4 per cent and 6.7 per cent during 2005 and 2006 respectively. In 2005 Cataflam® D 50mg, Coxflam® 15mg, Coxflam® 7.5mg and Arthrotec® were in second to fifth place according to cost and represented 9.6 per cent, 8.8 per cent, 3.3 per cent and 3.1 per cent respectively. In 2006 Coxflam® 15mg, Cataflam® D 50mg, Dicloflam® blackcurrent and another Coxib, Prexige® 100mg were in second to fifth places according to cost and represented 10.3 per cent, 5.8 per cent, 3.8 per cent and 3.8 per cent respectively.

In 2005 and 2006, females accounted for approximately 61 per cent of all NSAID medicine items (refer to paragraph 4.3.2.8), and approximately 66 per cent of the cost of all NSAID medicine items claimed, compared to males who accounted for only approximately 39 per cent of all NSAID medicine items and approximately 34 per cent of the cost of all NSAID medicine items. This indicates that the female population used approximately 22 per cent more NSAID medicine items than the male population, while accounting for approximately 31 per cent more of the cost during both 2005 and 2006, and also showed greater use of Coxibs such as Celebrex® 200mg among females (n=47 911) compared to males (n=20 034). There was no practical significant difference in the average cost per NSAID medicine item between female and male patients.

The top NSAID medicine item dispensed to females during 2005 (refer to paragraph 4.3.2.8) was Celebrex® 200mg (n=47 911) with a CPI of 3.32 and was followed by Coxflam® 15mg with a CPI of 1.12, compared to the male population where the NSAID medicine item dispensed most was Cataflam® D 50mg tablets (n=31 057) with a CPI of 1.49 and was also followed by Coxflam® 15mg with a CPI of 2.16.

The top NSAID medicine item dispensed to both females and males during 2006 was Coxflam® 15mg tablets with a prevalence of 9 per cent of NSAID medicine items among the female population and a prevalence of 6.3 per cent of NSAID medicine items among the male population. Celebrex® 200mg and Cataflam® D 50mg was second in 2006 among the female and male populations respectively.

- ***The ninth specific objective was to identify and analyse the number of NSAID containing prescriptions per patient for medicine claim database M.***

The average number of general prescriptions remained constant at an average of 7 prescriptions per patient for both 2005 and 2006 (refer to paragraph 4.3.2.5). Similarly the average number of NSAID prescriptions per patient also remained constant at an average of approximately 2 prescriptions per patient for both 2005 and 2006. Analysis showed that approximately 26 per cent of patients received three or more NSAID prescriptions per year for both 2005 and 2006 (refer to table 4.9). Conditions such as rheumatoid arthritis and osteoarthritis are chronic conditions and should receive six or more prescriptions per year. According to the data in table 4.9 only approximately 8.4 % of patients on medical schemes claimed six or more NSAID prescriptions per year during 2005 and 2006. This might be because only rheumatoid arthritis was on the Chronic Disease List and could be claimed as a prescribed minimum benefit (refer to paragraph 2.2.3). It might also be that some of the NSAIDs prescribed were not listed on the medical aid formularies and the patients paid cash for their chronic prescriptions, not claiming them through the medical scheme.

- ***The tenth specific objective was to identify the prevalence of NSAID use according to active ingredient for medicine claim database M.***

The analysis of the combined data (2005 and 2006) for NSAID active ingredients revealed that diclofenac was the active ingredient most prescribed during the study period and accounted for 40 per cent of the prevalence of all NSAIDs, followed by meloxicam with 18 per cent and ibuprofen with 10 per cent, while celecoxib had a prevalence of 9 per cent for the study period (refer to paragraph 4.3.2.8 and figure 4.22). This revealed similar results as a study performed by Thompson *et al.* (2005:1309), where they found that diclofenac (38 %) in various forms was the commonest prescribed drug, followed by ibuprofen (24 %) and meloxicam (9 %). The data from medicine claim database M, however, showed that meloxicam was the second most prescribed active ingredient with a prevalence of approximately 18 per cent in both 2005 and 2006, compared to ibuprofen with a prevalence of approximately 10 per cent during the same period. The increased use of meloxicam rather than ibuprofen might be due to prescribers' perception of the safety and gastro-intestinal side-effects (refer to paragraph 2.1.5.1) associated with ibuprofen. The national prescribing centre (NPC, 2007:2) also stated that 46 per cent of all NSAIDs prescribed in England from April to June 2007 was diclofenac, 25 per cent ibuprofen, 6.5 per cent meloxicam, and only 3.1 per cent for celecoxib. Products containing diclofenac as active ingredient show an average cost ranging from approximately R3.00 (CPI of 0.05) to R144.00 (CPI of 2.29)

according to table C.1.1 (Appendix C). Thus in this study the use of diclofenac in various forms was similar to the results of the national prescribing centre (NPC, 2007:2) and Thompson *et al.* (2005:1309).

- ***The eleventh specific objective was to investigate the prevalence and cost of NSAID medicine items according to age for medicine claim database M.***

Age group one ($0 \leq 9$ years) had a prevalence of 1.7 per cent, and accounted 0.93 per cent of the total cost of all NSAID medicine items in 2005. Age group two ($9 \leq 19$ years) demonstrated a prevalence of 4.6 per cent and accounted for approximately 2.4 per cent of the total cost of all NSAID medicine items in 2005. Age group three ($19 \leq 45$ years) had the highest prevalence in 2005 with 33.8 per cent but only represented approximately 23 per cent of the total cost of all NSAIDs for 2005. Age group four ($45 \leq 59$ years) had a prevalence of 29.4 per cent but represented approximately 27.6 per cent of the total cost of all NSAIDs for 2005. Similarly, age group five (older than 59 years) had a prevalence of 30.4 per cent, more than three per cent lower than that of age group three but represented approximately twice (45 per cent) the cost of age group three for 2005. Age group five (older than 59 years) represented almost 46 per cent of the total cost of all NSAID medicine items for 2005 due to the relative high prevalence of Coxibs (sub-pharmacological group 4.1.3) in this age group.

Similar trends in prevalence were indicated for 2005 and 2006, with a prevalence of 1.6 per cent and 4.6 per cent for age groups one ($0 \leq 9$ years) and two ($9 \leq 19$ years) respectively, representing 0.9 per cent and 2.3 per cent of the total cost of NSAIDs during 2006. Age group three ($19 \leq 45$ years) still had the highest prevalence in 2006 with 33.1 per cent but only represented approximately 22 per cent of the total cost of all NSAIDs for 2006. Age group four ($45 \leq 59$ years) and five (older than 59 years) both had a prevalence of approximately 30 per cent and represented approximately 28 per cent and 47 per cent of the total cost of all NSAIDs for 2006 respectively. In age group five (older than 59 years) Coxibs represented 21 per cent of the prevalence, but 45 per cent of the cost.

The cost prevalence indices (CPIs) of NSAIDs prescribed for patients in age groups one to four were all below one for the years 2005 and 2006, indicating the relative inexpensiveness of NSAID therapy in these age groups. However, NSAIDs prescribed for patients in age group five had a CPI above one for both years indicating the relative expensiveness of NSAID therapy in this age group, mainly due to the high prevalence of Coxibs in this age group.

5.3 LIMITATIONS

The following shortcomings or limitations should be taken into account when evaluating the results and conclusions of this study:

- All the information and data available on both medicine claim databases, that were utilised in this study, were considered to be accurate and correct.
- No clinical data were available on the database thus patient compliance, side-effects and costs associated with hospitilisations due to gastro-intestinal complications related to NSAID use could not be measured.
- The cost amounts and percentages derived from each medicine claim database are only valid for that specific medicine claim database. Therefore it may not reflect the true usage patterns and costs associated with NSAID use in the total private health care sector of South Africa.
- Due to the nature and extent of the study, with reference to the general and specific objectives (refer to paragraph 1.3.2) to investigate the related usage and cost patterns of the active ingredients of NSAIDs, the effect of possible substitution of generic equivalents was not investigated. This may have had an influence on cost-related aspects and may be regarded as a limitation of the study.
- The ICD-10 codes indicated on the medicine claim database were not very specific, and limited the classification of NSAID usage according to disease.
- Some of the tables will not add up to one hundred per cent because percentages were rounded off to two decimals or the nearest rand.
- The average cost and total cost for Bextra® amounted to no more than a few cents on medicine claim database M during 2006. This could not be changed and would be reflected in the data.
- The datasets were verified by performing randomised data checks and outlined data testing.
- No demographic data, such as age and gender, were available on Medicine claim database I.

5.4 RECOMMENDATIONS

After completion of the research study, the following recommendation can be made:

- To investigate the possible substitution of Coxibs (sub-pharmacological group 4.1.3), that had the highest average cost per medicine item and represented a third to half of the cost for NSAID medicine items, for possibly more cost-effective NSAIDs such as selective-COX-2 inhibitors, or COX-inhibitors in combination with proton-pump inhibitors (PPI).

- To investigate the influence of innovator and generic medicine products and substitution on NSAID medicine use and related cost, as well as possible cost-saving through a cost-minimisation study (refer to paragraph 2.2.4.5.3).
- To investigate not only the safety of Coxibs, and NSAIDs in long-term use, but also to adress economical outcomes, as well as costs.
- To investigate the prevalence and cost of combination use of NSAIDs with gastro-protective drugs such as PPIs and compared to Coxib therapy.
- In this study there was significant evidence suggesting that after the withdrawal of Coxibs such as Vioxx®, patients replaced their Coxibs with COX-inhibitors. To investigate the COX-inhibitors (e.g. diclofenac) that these Coxibs were substituted with.
- Prescribers and providers of NSAID medicine items should be investigated to determine prescribing trends.
- In this study between 50 and 66 Coxib products were claimed through medicine claim database M in age group one ($0 \leq 9$ years) during 2005 and 2006 respectively. It is recommended that the relatively large variety of Coxibs used in age group one (patients younger than nine years) be investigated further.

5.5 CHAPTER SUMMARY

In this chapter the conclusions of the specific aims of the study were discussed. The recommendations that were formed from the study and its conclusions were also discussed in this chapter.

APPENDIX A

A.1 The pharmacological classification list.

1. CENTRAL NERVOUS SYSTEM
    - 1.1 Central nervous system stimulants
        - 1.1.1 Central analeptics
        - 1.1.2 Respiratory stimulants
        - 1.1.3 Others
    - 1.2 Sedative hypnotics
        - 1.2.1 Benzodiazepines
        - 1.2.2 Barbiturates
        - 1.2.3 Others
    - 1.3 Anxiolytics
        - 1.3.1 Benzodiazepines (1.2.1)
        - 1.3.2 Others
    - 1.4 Anti-depressants
        - 1.4.1 Tricyclic
        - 1.4.2 Non-Tricyclic
        - 1.4.3 Mono-Amine Oxidase inhibitors
            - 1.4.3.1 Non-selective mono-amine oxidase inhibitors
            - 1.4.3.2 Selective mono-amine oxidase inhibitors
        - 1.4.4 Selective serotonin re-uptake inhibitors
        - 1.4.5 Serotonin and noradrenaline re-uptake inhibitors
        - 1.4.6 Lithium
        - 1.4.7 Others
    - 1.5 Anti-psychotics
        - 1.5.1 Phenothiazines
        - 1.5.2 Butyrophenones
        - 1.5.3 Others
    - 1.6 Anti-epileptics
    - 1.7 Anti-Parkinson agents
        - 1.7.1 Dopaminergics
        - 1.7.2 Anticholinergics
        - 1.7.3 Others

- 1.8 Anti-vertigo and anti-emetic agents
- 1.9 Anti-migraine agents
- 1.10 Alzheimer's disease

2. ANAESTHETICS
   - 2.1 General anaesthetics
     - 2.1.1 Inhalation anaesthetics
     - 2.1.2 Parenteral anaesthetics
   - 2.2 Local anaesthetics
     - 2.2.1 Surface anaesthetics
   - 2.3 Muscle relaxants
3. ANALGESICS
   - 3.1 Narcotic analgesics
   - 3.2 Analgesics and antipyretics
   - 3.3 Combinations
   - 3.4 Others
4. MUSCULO-SKELETAL AGENTS
   - 4.1 Non-steroidal anti-inflammatory agents (3.2 and 4.3)
     - 4.1.1 COX inhibitors
     - 4.1.2 Selective COX2 inhibitors
     - 4.1.3 Specific cyclo-oxygenase-2 inhibitor (COXIB)
   - 4.2 Anti-gout
   - 4.3 Topical agents
   - 4.4 Gold
   - 4.5 Centrally acting muscle relaxants
   - 4.6 Others
   - 4.7 Osteoporosis (and other metabolic bone disorders)
     - 4.7.1 Bisphosponates
     - 4.7.2 Selective oestrogen receptor modulators
     - 4.7.3 Calcitonin
     - 4.7.4 Minerals and vitamin D
     - 4.7.5 Dual action bone agents
5. AUTONOMIC
   - 5.1 Sympathomimetics (7.6, 10.1.2)
   - 5.2 Sympatholytics (7.2, 7.3, 7.4)
   - 5.3 Cholinergics

5.4 Anti-cholinergics (1.7.2, 12.3)

5.5 Others

6. AUTACOIDS

6.1 Anti-histamines (10.1.1, 10.1.3, 14.9)

6.2 Serotonin antagonists

6.3 NK1 Antagonists

7. CARDIO-VASCULAR AGENTS

7.1 Positive inotropic agents

7.1.1 Cardiac glycosides

7.1.2 Others (5.1)

7.2 Anti-arrhytmics

7.3 Anti-hypertensives (Single agents and combinations including diuretic combinations)

7.3.1 Central acting sympathetic system inhibitors

7.3.2 Alpha-receptor blockers

7.3.3 Beta-receptor blockers

7.3.4 Alpha- and Beta-receptor blockers

7.3.5 Sympathetic nervous blockers

7.3.6 Direct acting vasodilators

7.3.7 Calcium channel blockers

7.3.8 ACE inhibitors

7.3.9 Angiotension receptor antagonists

7.3.10 Others

7.4 Anti-anginal agents

7.4.1 Calcium channel blockers

7.4.2 Beta-receptor blockers

7.4.3 Organic nitrates

7.5 Other vasodilators

7.5.1 After-load reducers

7.5.2 Peripheral vasodilators

7.6 Vasoconstrictors

7.7 Hipolipidaemic agents

7.7.1 Fibrates

7.7.2 HMG-CoA reductase inhibitors (Statins)

7.7.3 Cholesterol absorption inhibitors

7.7.4 Others

- 7.8 Plasma expanders

8. BLOOD AND HAEMOPOEITIC
    - 8.1 Haemostatics
    - 8.2 Antocoagulants
    - 8.3 Fibrinolytics
    - 8.4 Platelet aggregation inhibitors
    - 8.5 Sclerosing agents
    - 8.6 Haematinics (20.3)
    - 8.7 Others
9. ALCOHOLISM
10. RESPIRATORY SYSTEM
    - 10.1 Coughs and colds
        - 10.1.1 Antitussives and expectorants
        - 10.1.2 Decongestant, analgesic combinations
        - 10.1.3 Decongestants (6.1)
    - 10.2 Broncodilators
        - 10.2.1 Sympathomimetics
        - 10.2.2 Methylxanthines
        - 10.2.3 Anticholinergics
        - 10.2.4 Combinations
    - 10.3 Mucolytics
    - 10.4 Anti-asthmatics
        - 10.4.1 Glucocorticoids
        - 10.4.2 Leukotriene receptor antagonist
        - 10.4.3 Chromones
        - 10.4.4 Other anti-asthmatics
    - 10.5 Surfactants
    - 10.6 Others
11. EAR, NOSE AND THROAT
    - 11.1 Topical and nasal preparations
        - 11.1.1 Antimicrobial and combinations
        - 11.1.2 Glucocorticosteroids
        - 11.1.3 Chromones
        - 11.1.4 Decongestants
        - 11.1.5 Antihistamines

- 11.1.6 Mucolytics
- 11.1.7 Others
- 11.2 Ear drops and ointments
- 11.3 Mouth and throat reparations

12. GASTRO-INTESTINAL TRACT
    - 12.1 Digestants
    - 12.2 Appetite suppressants
    - 12.3 Anti-spasmodics (1.8, 5.4, 12.4.2)
    - 12.4 Acid reducers
        - 12.4.1 Antacids
        - 12.4.2 Antacids and combinations
        - 12.4.3 Histamine-2 receptor antagonist
        - 12.4.4 Proton pump inhibitors
        - 12.4.5 Cytoprotective agents
        - 12.4.6 Other acid reducers
    - 12.5 Motility enhancers
    - 12.6 Laxatives
    - 12.7 Antidiarrhoeals
    - 12.8 Liver, gall bladder and bile
    - 12.9 Suppositories and anal ointments
    - 12.10 Others
13. ANTHELMINTICS
14. DERMATOLOGIGALS
    - 14.1 Anti-bacterial antiseptic agents
    - 14.2 Anti-parasitics
    - 14.3 Fungicides
    - 14.4 Cortico-steroids
        - 14.4.1 Cortico-steroids with anti-infective agents
    - 14.5 Psoriasis (14.4 , 23)
    - 14.6 Acne (18.4)
    - 14.7 Melanin inhibitors and stimulants
    - 14.8 Emolients and protectives
    - 14.9 Others
15. OPHTHALMICS
    - 15.1 Anti-infectives

- 15.1.1 Antivirals
- 15.2 Corticosteroids
- 15.3 Combinations (anti infectives with corticosteroids)
- 15.4 Decongestants
- 15.5 Mydriatics
- 15.6 Glaucoma
- 15.7 Others

16. URINARY SYSTEM
    - 16.1 Diuretics
    - 16.2 Anti-diuretics
    - 16.3 Urinary alkanizers
    - 16.4 Urinary antiseptics
    - 16.5 Others (5.3, 5.4)
17. GENITAL SYSTEM
    - 17.1 Contraceptives
        - 17.1.1 Hormonal (including oral)
        - 17.1.2 Locally acting
        - 17.1.3 Contraceptive devices
    - 17.2 Vaginal preparations (19.6.2)
    - 17.3 Oxytocics
    - 17.4 Uterine antispasmodics
    - 17.5 Sexual dysfunction
        - 17.5.1 Others
        - 17.5.2 Erectile dysfunction
18. ANTI-MICROBIALS
    - 18.1 Beta-lactams
        - 18.1.1 Penicillins
        - 18.1.2 Cephalosporins
        - 18.1.3 Others
    - 18.2 Erythromycin and other macrolides
    - 18.3 Aminoglycosides
    - 18.4 Tetracyclines
    - 18.5 Chloramphenicols
    - 18.6 Sulphonamides and combinations
    - 18.7 Quinolones

18.8 Mycobacteria

18.8.1 Tuberculostatics (18.7)

18.8.2 Anti-leprotics

18.9 Other anti-bacterial agents

18.10 Anti-fungal agents

18.11 Anti-protozoal agents

18.12 Anti-viral agents

19. ENDOCRINE SYSTEM

19.1 Anti-diabetic agents

19.1.1 Insulins

19.1.2 Oral agents

19.2 Anti-hypoglycaemic agents

19.3 Thyroid

19.4 Parathyroid and calcitonin

19.5 Corticosteroids (12.9, 14.4, 14.4.1, 15.2)

19.6 Sex hormones

19.6.1 Androgens and anabolic steroids

19.6.2 Oestrogens (19.6.4)

19.6.3 Progestogens (19.6.4)

19.6.4 Combinations (17.1.1, 19.6.2, 19.6.3)

19.6.5 Others

19.7 Tropic hormones

19.8 Hormone inhibitors

20. VITAMINS, TONICS, MINERALS AND ELECTROLYTES

20.1 Vitamins

20.1.1 Vitamin combinations

20.2 Vitamins with minerals

20.3 Tonics (8.6)

20.4 Minerals and electrolytes

21. AMINO-ACIDS

22. SPECIAL FOODS

23. CYTOSTATICS (19.6.3, 19.8)

24. IMMUNOLOGICAL

24.1 Immunosuppressants

24.2 Immunostimulants

25. CHELATING AGENTS, ION EXCHANGE PREPARATIONS
26. BIOLOGICALS
27. ENZYMES (8.3, 12.1, 12.6)
28. POISON ANTIDOTES
29. OTHERS
30. MEDICAL GAS

APPENDIX B

1. Tables of Database I

Table B.1.1 The prevalence of different sub-pharmacological groups for 2004 to 2006

Prevalence of different sub-pharmacological groups for 2004-2006 (Database I)								
Year	**Term**	**Pharm-code**	**Active ingredient**	**Prevalence (n)**	**Percent (%)**	**Average cost per medicine item (R)**	**Total cost (R)**	**Cost percent-age (%)**
2004	**1**	**4.1.1**	Diclofenac	24895	38.82	84.86 (±66.74)	2112115.85	24.14
			Diclofenac/ misoprostol	1920	2.99	185.82 (±92.55)	356771.65	4.08
			Diflunisal	1	0.00	180.84 (±)	180.84	0.00
			Flurbiprofen	3	0.00	182.84 (±97.90)	548.53	0.01
			Ibuprofen	4819	7.51	34.99 (±54.30)	168628.73	1.93
			Indomethacin	1782	2.78	67.04 (±85.74)	119469.02	1.37
			Ketoprofen	733	1.14	118.48 (±80.50)	86846.75	0.99
			Lornoxicam	1098	1.71	121.76 (±77.95)	133693.35	1.53
			Nabumetone	172	0.27	157.59 (±64.58)	27106.32	0.31
			Naproxen	2698	4.21	159.23 (±128.39)	429609.57	4.91
			Phenylbutazone	54	0.08	28.03 (±15.80)	1513.54	0.02
			Piroxicam	3643	5.68	92.74 (±36.14)	337870.84	3.86
			Sulindac	47	0.07	190.10 (±100.78)	8934.76	0.10
			Tenoxicam	132	0.21	219.74 (±197.0)	29006.21	0.33
			Tiaprofenic acid	1	0.00	587.07 (±)	587.07	0.01
		4.1.2	Meloxicam	7705	12.01	103.19 (±61.43)	795098.16	9.09
		4.1.3	Celecoxib	5317	8.29	321.62 (±139.73)	1710058.09	19.54

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Parecoxib	4	0.01	188.21 (±183.61)	752.85	0.01
			Rofecoxib	9108	14.20	266.96 (±140.08)	2431509.72	27.79
	Total term 1			64132	26.73	136.44 (±126.06)	8750301.85	33.73
	2	**4.1.1**	Diclofenac	37278	42.74	79.09 (±68.87)	2945987.53	33.10
			Diclofenac/ misoprostol	2053	2.35	159.46 (±78.13)	327381.92	3.68
			Flurbiprofen	4	0.00	233.53 (±92.39)	934.11	0.01
			Ibuprofen	7074	8.11	27.95 (±47.18)	197753.42	2.22
			Indomethacin	2493	2.86	46.31 (±62.35)	115448.87	1.30
			Ketoprofen	873	1.00	122.91 (±91.91)	107300.39	1.21
			Lornoxicam	1050	1.20	99.62 (±64.76)	104605.84	1.18
			Nabumetone	196	0.22	129.39 (±61.81)	25359.76	0.28
			Naproxen	3331	3.82	113.66 (±96.96)	378603.75	4.25
			Phenylbutazone	55	0.06	27.13 (±13.63)	1492.19	0.02
			Piroxicam	4656	5.34	65.52 (±46.55)	305070.08	3.43
			Sulindac	59	0.07	174.52 (±66.58)	10296.85	0.12
			Tenoxicam	89	0.10	265.37 (±154.69)	23617.82	0.27
			Tiaprofenic acid	2	0.00	338.20 (±315.81)	676.40	0.01
		4.1.2	Meloxicam	10142	11.63	75.61 (±56.63)	766816.50	8.62
		4.1.3	Celecoxib	5474	6.28	262.61 (±127.36)	1437551.41	16.15
			Parecoxib	5	0.01	82.33 (±13.05)	411.67	0.00
			Rofecoxib	11724	13.44	254.50 (±133.01)	2983742.31	33.52
			Valdecoxib	667	0.76	101.10 (±60.83)	67434.60	0.76

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
	Total term 2			87225	36.35	112.36 (±112.16)	8900485.42	34.31
	3	**4.1.1**	Diclofenac	37908	42.79	63.42 (±59.37)	2402351.88	32.50
			Diclofenac/ misoprostol	2411	2.72	129.83 (±62.87)	313030.27	4.23
			Flurbiprofen	1	0.00	248.28 (±)	248.28	0.00
			Ibuprofen	6027	6.80	25.63 (±47.88)	154499.45	2.09
			Indomethacin	2620	2.96	31.94 (±43.98)	83681.02	1.13
			Ketoprofen	989	1.12	75.48 (±51.84)	74651.33	1.01
			Lornoxicam	1208	1.36	77.63 (±48.31)	93783.72	1.27
			Nabumetone	198	0.22	102.27 (±47.56)	20250.04	0.27
			Naproxen	3442	3.89	95.63 (±72.99)	329171.46	4.45
			Oxaprosin	1	0.00	123.11 (±)	123.11	0.00
			Phenylbutazone	56	0.06	24.60 (±12.84)	1377.37	0.02
			Piroxicam	5067	5.72	33.20 (±24.13)	168208.25	2.28
			Sulindac	85	0.10	149.22 (±50.28)	12683.83	0.17
			Tenoxicam	81	0.09	333.35 (±226.38)	27001.72	0.37
			Tiaprofenic acid	1	0.00	441.42 (±)	441.42	0.01
		4.1.2	Meloxicam	12847	14.50	54.92 (±37.70)	705585.55	9.55
		4.1.3	Celecoxib	8747	9.87	207.21 (±106.71)	1812428.57	24.52
			Parecoxib	15	0.02	99.84 (±110.28)	1497.60	0.02
			Rofecoxib	3574	4.03	229.37 (±122.50)	819756.28	11.09
			Valdecoxib	3303	3.73	112.45 (±75.42)	371428.40	5.02
	Total term 3			88581	36.92	88.45 (±87.23)	7392199.55	28.49
Total year 2004				239938	100.00	108.12 (±109.89)	25942986.82	100.00
2005	**4**	**4.1.1**	Diclofenac	27931	54.39	67.33 (±62.61)	1876871.96	47.26

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Diclofenac/ misoprostol	1021	1.99	131.10 (±69.62)	133852.43	3.37
			Ibuprofen	3762	7.33	25.40 (±47.84)	95574.94	2.41
			Indomethacin	1406	2.74	33.22 (±47.26)	46714.90	1.18
			Ketoprofen	448	0.87	86.84 (±29.68)	38905.50	0.98
			Lornoxicam	699	1.36	78.31 (±48.40)	54739.40	1.38
			Nabumetone	72	0.14	113.05 (±61.26)	8139.86	0.20
			Naproxen	1636	3.19	90.81 (±69.91)	148563.62	3.74
			Phenylbutazone	27	0.05	23.77 (±14.44)	641.87	0.02
			Piroxicam	2745	5.35	33.13 (±24.07)	90943.01	2.29
			Sulindac	21	0.04	153.17 (±69.73)	3216.64	0.08
			Tenoxicam	34	0.07	403.70 (±257.84)	13725.97	0.35
		4.1.2	Meloxicam	6481	12.62	57.59 (±38.51)	373240.96	9.40
		4.1.3	Celecoxib	3684	7.17	248.14 (±126.13)	914162.22	23.02
			Parecoxib	3	0.01	84.80 (±41.30)	254.41	0.01
			Rofecoxib	2	0.00	243.85 (±234.0)	487.71	0.01
			Valdecoxib	1380	2.69	123.99 (±113.54)	171103.99	4.31
	Total term 4			51352	32.51	77.33 (±84.63)	3971139.39	34.09
	5	**4.1.1**	Diclofenac	33619	57.32	59.77 (±57.45)	2005293.15	48.32
			Diclofenac/ misoprostol	1116	1.90	128.70 (±64.28)	143633.51	3.46
			Ibuprofen	4269	7.28	25.26 (±45.46)	107818.16	2.60
			Indomethacin	1766	3.01	32.43 (±46.98)	57273.05	1.38
			Ketoprofen	532	0.91	91.13 (±47.09)	48482.30	1.17
			Lornoxicam	831	1.42	83.16 (±51.66)	69108.93	1.67
			Nabumetone	74	0.13	111.80 (±52.96)	8273.61	0.20

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Naproxen	1781	3.04	85.05 (±63.53)	151480.81	3.65
			Phenylbutazone	20	0.03	36.24 (±11.41)	724.84	0.02
			Piroxicam	3246	5.53	31.75 (±19.96)	103048.54	2.48
			Sulindac	17	0.03	151.22 (±31.30)	2570.75	0.06
			Tenoxicam	34	0.06	263.43 (±270.94)	8956.52	0.22
		4.1.2	Meloxicam	7210	12.29	62.32 (±39.92)	449338.96	10.83
		4.1.3	Celecoxib	4096	6.98	241.45 (±127.60)	988972.03	23.83
			Parecoxib	20	0.03	68.73 (±20.47)	1374.65	0.03
			Valdecoxib	17	0.03	192.05 (±201.56)	3264.94	0.08
	Total term 5			58648	37.12	70.75 (±79.24)	4149614.75	35.62
	6	**4.1.1**	Diclofenac	28310	59.01	55.40 (±50.57)	1565912.38	44.38
			Diclofenac/ misoprostol	839	1.75	137.82 (±68.38)	115634.79	3.28
			Ibuprofen	2796	5.83	24.33 (±39.75)	68035.93	1.93
			Indomethacin	1139	2.37	43.31 (±57.03)	49335.95	1.40
			Ketoprofen	406	0.85	93.75 (±57.49)	38062.10	1.08
			Lornoxicam	602	1.25	92.15 (±60.05)	55476.71	1.57
			Nabumetone	47	0.10	130.87 (±54.18)	6150.75	0.17
			Naproxen	1200	2.50	98.11 (±60.74)	117734.23	3.34
			Phenylbutazone	17	0.04	37.19 (±18.53)	632.25	0.02
			Piroxicam	2426	5.06	33.10 (±21.25)	80309.34	2.28
			Sulindac	20	0.04	146.05 (±77.40)	2921.11	0.08
			Tenoxicam	8	0.02	442.87 (±325.35)	3542.97	0.10
		4.1.2	Meloxicam	6091	12.70	65.27 (±39.10)	397574.82	11.27
		4.1.3	Celecoxib	4056	8.45	252.98 (±123.18)	1026091.69	29.08

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Parecoxib	16	0.03	65.62 (±12.0)	1049.87	0.03
			Valdecoxib	2	0.00	66.04 (±)	132.08	0.00
	Total term 6			47975	30.37	73.55 (±82.11)	3528596.97	30.29
Total year 2005				157975	100.00	73.74 (±81.94)	11649351.11	100.00
2006	7	**4.1.1**	Diclofenac	23836	66.12	48.57 (±45.94)	1154549.04	45.57
			Diclofenac/ misoprostol	328	0.91	138.27 (±71.09)	45352.62	1.79
			Ibuprofen	2106	5.84	30.06 (±54.57)	63303.24	2.50
			Indomethacin	809	2.24	36.63 (±53.01)	29637.10	1.17
			Ketoprofen	206	0.57	100.37 (±47.19)	20676.36	0.82
			Lornoxicam	271	0.75	126.53 (±61.07)	34289.51	1.35
			Nabumetone	10	0.03	105.86 (±35.92)	1058.64	0.04
			Naproxen	717	1.99	79.07 (±64.97)	56695.04	2.24
			Phenylbutazone	11	0.03	30.33 (±12.64)	333.64	0.01
			Piroxicam	1703	4.72	29.20 (±14.81)	49727.31	1.96
			Sulindac	3	0.01	151.26 (±85.12)	453.79	0.02
			Tenoxicam	9	0.02	468.41 (±339.12)	4215.70	0.17
		4.1.2	Meloxicam	3315	9.20	73.73 (±41.61)	244429.44	9.65
		4.1.3	Celecoxib	2718	7.54	305.52 (±138.35)	830412.86	32.78
			Parecoxib	6	0.02	63.51 (±14.07)	381.05	0.02
	Total term 7			36048	32.03	70.34 (±90.79)	2535515.34	31.41
	8	**4.1.1**	Diclofenac	25347	65.90	45.23 (±42.39)	1140580.74	44.01
			Diclofenac/ misoprostol	381	0.99	140.16 (±76.37)	53401.32	2.06
			Ibuprofen	2481	6.45	28.62 (±57.54)	71001.30	2.74
			Indomethacin	767	1.99	40.86 (±55.60)	31342.33	1.21

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Ketoprofen	144	0.37	107.24 (±65.86)	15442.98	0.60
			Lornoxicam	232	0.60	115.80 (±56.92)	26866.52	1.04
			Nabumetone	49	0.13	87.29 (±37.89)	4277.16	0.17
			Naproxen	697	1.81	77.32 (±62.26)	53893.40	2.08
			Phenylbutazone	9	0.02	35.44 (±5.34)	318.96	0.01
			Piroxicam	1733	4.51	28.71 (±16.80)	49750.99	1.92
			Sulindac	13	0.03	135.08 (±66.92)	1756.07	0.07
			Tenoxicam	19	0.05	294.76 (±287.39)	5600.36	0.22
		4.1.2	Meloxicam	3296	8.57	72.74 (±40.91)	239755.03	9.25
		4.1.3	Celecoxib	2866	7.45	291.70 (±123.24)	836026.62	32.26
			Lumiracoxib	412	1.07	147.71 (±97.98)	60857.14	2.35
			Parecoxib	14	0.04	64.70 (±17.59)	905.87	0.03
	Total term 8			38460	34.17	67.39 (±86.52)	2591776.79	32.10
	9	**4.1.1**	Diclofenac	23244	61.12	43.65 (±41.47)	1010926.50	34.32
			Diclofenac/ misoprostol	319	0.84	135.09 (±68.11)	43093.30	1.46
			Ibuprofen	2114	5.56	31.33 (±62.31)	66228.07	2.25
			Indomethacin	611	1.61	48.25 (±73.57)	29484.10	1.00
			Ketoprofen	127	0.33	106.00 (±53.94)	13461.98	0.46
			Lornoxicam	277	0.73	107.39 (±57.28)	29748.33	1.01
			Nabumetone	7	0.02	100.81 (±28.26)	705.65	0.02
			Naproxen	509	1.34	79.50 (±64.95)	40465.16	1.37
			Phenylbutazone	8	0.02	34.55 (±13.47)	276.44	0.01
			Piroxicam	1569	4.13	29.67 (±15.86)	46558.83	1.58
			Sulindac	20	0.05	128.92 (±47.34)	2578.47	0.09

Table B.1.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Tenoxicam	16	0.04	297.77 (±287.82)	4764.31	0.16
		4.1.2	Meloxicam	2873	7.55	76.50 (±43.73)	219784.28	7.46
		4.1.3	Celecoxib	2343	6.16	295.62 (±117.09)	692628.46	23.51
			Lumiracoxib	3955	10.40	187.51 (±108.36)	741595.19	25.18
			Parecoxib	41	0.11	83.99 (±73.19)	3443.54	0.12
	Total term 9			38033	33.79	77.45 (±94.46)	2945742.61	36.49
Total year 2006				112541	100.00	71.73 (±90.73)	8073034.74	100.00

2. Tables of Database M

Table B.2.1 The prevalence of different sub-pharmacological groups 2005 to 2006

Frequency of different sub-pharmacological groups for Database M 2005-2006								
Year	**Term**	**Pharm-code**	**Active ingredient**	**Prevalence (n)**	**Percent (%)**	**Average cost per medicine item (R)**	**Total cost (R)**	**Cost percent-age (%)**
2005	**4**	**4.1.1**	Diclofenac	107978	36.83	46.45 (±48.77)	5015450.35	24.85
			Diclofenac/ misoprostol	9307	3.17	133.79 (±56.80)	1245184.11	6.17
			Ibuprofen	29872	10.19	22.85 (±34.50)	682684.24	3.38
			Indomethacin	11514	3.93	34.42 (±48.04)	396373.43	1.96
			Ketoprofen	3140	1.07	82.64 (±32.62)	259495.82	1.29
			Lornoxicam	4932	1.68	76.95 (±50.81)	379543.95	1.88
			Nabumetone	664	0.23	103.58 (±45.12)	68779.57	0.34
			Naproxen	13169	4.49	76.39 (±67.04)	1006010.63	4.99
			Phenylbutazone	130	0.04	19.88 (±10.10)	2584.50	0.01
			Piroxicam	20573	7.02	33.39 (±24.87)	686936.50	3.40
			Sulindac	341	0.12	138.25 (±53.81)	47144.75	0.23
			Tenoxicam	521	0.18	107.45 (±119.35)	55982.44	0.28
		4.1.2	Meloxicam	53498	18.25	60.11 (±37.88)	3215617.47	15.94
		4.1.3	Celecoxib	25933	8.84	218.20 (±72.84)	5658571.29	28.04
			Parecoxib	431	0.15	69.12 (±62.30)	29790.38	0.15
			Rofecoxib	21	0.01	143.91 (±130.21)	3022.16	0.01
			Valdecoxib	11178	3.81	127.58 (±86.99)	1426120.10	7.07
	Total term 4			293202	31.81	68.82 (±73.74)	20179291.69	34.62
	5	**4.1.1**	Diclofenac	138233	42.26	41.47 (±45.48)	5732606.40	28.81
			Diclofenac/ misoprostol	9301	2.84	133.90 (±57.46)	1245372.49	6.26
			Flurbiprofen	1	0.00	73.53 (±)	73.53	0.00
			Ibuprofen	35170	10.75	22.34 (±33.20)	785626.57	3.95

Table B.2.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Indomethacin	12776	3.91	33.90 (±48.06)	433076.56	2.18
			Ketoprofen	3066	0.94	81.98 (±33.97)	251346.49	1.26
			Lornoxicam	6113	1.87	72.30 (±50.19)	441947.40	2.22
			Meclofenamic acid	3	0.00	91.33 (±75.28)	273.98	0.00
			Nabumetone	743	0.23	97.91 (±46.55)	72743.98	0.37
			Naproxen	14652	4.48	67.74 (±59.75)	992512.99	4.99
			Phenylbutazone	157	0.05	20.44 (±10.94)	3209.17	0.02
			Piroxicam	22454	6.87	32.82 (±24.60)	736881.70	3.70
			Sulindac	344	0.11	134.56 (±50.96)	46288.89	0.23
			Tenoxicam	675	0.21	80.31 (±103.0)	54212.11	0.27
		4.1.2	Meloxicam	55741	17.04	59.73 (±37.85)	3329330.12	16.73
		4.1.3	Celecoxib	26869	8.22	212.75 (±77.61)	5716500.95	28.73
			Parecoxib	637	0.19	70.54 (±38.36)	44937.40	0.23
			Valdecoxib	128	0.04	76.65 (±79.80)	9811.65	0.05
	Total term 5			327063	35.48	60.83 (±68.39)	19896752.38	34.13
	6	**4.1.1**	Diclofenac	128228	42.52	37.87 (±40.59)	4855512.39	26.66
			Diclofenac/ misoprostol	8977	2.98	133.44 (±57.93)	1197885.83	6.58
			Flurbiprofen	1	0.00	105.29 (±)	105.29	0.00
			Ibuprofen	28373	9.41	22.00 (±30.41)	624339.51	3.43
			Indomethacin	11825	3.92	35.82 (±49.94)	423523.14	2.33
			Ketoprofen	2465	0.82	81.67 (±31.28)	201323.27	1.11
			Lornoxicam	5230	1.73	73.49 (±50.73)	384359.85	2.11
			Meclofenamic acid	1	0.00	67.42 (±)	67.42	0.00
			Nabumetone	618	0.20	99.15 (±45.91)	61277.75	0.34

Table B.2.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Naproxen	14213	4.71	67.36 (±59.88)	957351.20	5.26
			Phenylbutazone	166	0.06	21.96 (±11.31)	3645.37	0.02
			Piroxicam	20740	6.88	32.70 (±24.78)	678168.99	3.72
			Sulindac	298	0.10	129.72 (±52.09)	38655.44	0.21
			Tenoxicam	592	0.20	92.50 (±111.79)	54762.59	0.30
		4.1.2	Meloxicam	53804	17.84	61.27 (±37.30)	3296560.20	18.10
		4.1.3	Celecoxib	25251	8.37	213.11 (±75.35)	5381133.05	29.54
			Parecoxib	806	0.27	68.78 (±33.94)	55438.73	0.30
			Valdecoxib	10	0.00	25.85 (±75.90)	258.46	0.00
	Total term 6			301598	32.72	60.39 (±67.60)	18214368.48	31.25
Total year 2005				921863	100.00	63.23 (±69.80)	58290412.55	100.00
2006	**7**	**4.1.1**	Diclofenac	134727	41.73	38.47 (±40.57)	5183569.38	26.73
			Diclofenac/ misoprostol	9394	2.91	134.21 (±57.17)	1260791.15	6.50
			Ibuprofen	32332	10.01	20.97 (±32.47)	677914.11	3.50
			Indomethacin	13307	4.12	34.16 (±49.98)	454636.90	2.34
			Ketoprofen	2403	0.74	83.16 (±36.97)	199833.85	1.03
			Lornoxicam	4902	1.52	79.34 (±52.64)	388942.35	2.01
			Meclofenamic acid	2	0.00	87.39 (±7.56)	174.79	0.00
			Nabumetone	971	0.30	108.04 (±56.76)	104905.30	0.54
			Naproxen	14835	4.59	64.87 (±59.46)	962427.90	4.96
			Phenylbutazone	210	0.07	21.91 (±10.75)	4600.47	0.02
			Piroxicam	21445	6.64	32.76 (±24.17)	702601.59	3.62
			Sulindac	167	0.05	140.07 (±55.51)	23391.09	0.12
			Tenoxicam	571	0.18	110.71 (±121.61)	63217.28	0.33

Table B.2.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
		4.1.2	Meloxicam	60489	18.74	61.96 (±34.17)	3747897.02	19.32
		4.1.3	Celecoxib	26246	8.13	211.87 (±76.88)	5560681.23	28.67
			Parecoxib	849	0.26	70.93 (±48.29)	60219.40	0.31
			Valdecoxib	7	0.00	0.02 (±0.02)	0.14	0.00
	Total term 7			322857	33.83	60.07 (±67.21)	19395803.95	33.58
	8	**4.1.1**	Diclofenac	145431	42.03	36.04 (±39.38)	5241103.23	26.43
			Diclofenac/ misoprostol	9053	2.62	133.90 (±57.77)	1212218.00	6.11
			Ibuprofen	38034	10.99	19.61 (±29.88)	745886.56	3.76
			Indomethacin	14423	4.17	30.89 (±46.88)	445509.19	2.25
			Ketoprofen	2191	0.63	83.23 (±34.23)	182365.33	0.92
			Lornoxicam	5046	1.46	74.25 (±49.44)	374653.39	1.89
			Nabumetone	874	0.25	97.43 (±52.60)	85157.44	0.43
			Naproxen	15352	4.44	56.82 (±55.61)	872234.71	4.40
			Phenylbutazone	186	0.05	22.41 (±11.72)	4169.10	0.02
			Piroxicam	21684	6.27	31.33 (±23.57)	679360.13	3.43
			Sulindac	154	0.04	132.84 (±53.41)	20456.82	0.10
			Tenoxicam	718	0.21	93.00 (±120.53)	66771.51	0.34
		4.1.2	Meloxicam	60856	17.59	61.56 (±37.16)	3746471.02	18.90
		4.1.3	Celecoxib	26585	7.68	208.58 (±78.41)	5545236.39	27.97
			Lumiracoxib	4327	1.25	122.79 (±72.78)	531331.82	2.68
			Parecoxib	1136	0.33	65.82 (±49.38)	74772.99	0.38
	Total term 8			346050	36.26	57.30 (±66.15)	19827697.63	34.33
	9	**4.1.1**	Diclofenac	108813	38.14	37.20 (±40.73)	4047469.80	21.84
			Diclofenac/ misoprostol	7485	2.62	135.03 (±59.27)	1010731.76	5.45

Table B.2.1 (continue)

Year	Term	Pharm-code	Active ingredient	Prevalence (n)	Percent (%)	Average cost per medicine item (R)	Total cost (R)	Cost percent-age (%)
			Ibuprofen	24904	8.73	20.71 (±32.18)	515884.57	2.78
			Indomethacin	11284	3.95	29.54 (±45.35)	333293.24	1.80
			Ketoprofen	1695	0.59	82.10 (±36.61)	139160.49	0.75
			Lornoxicam	3829	1.34	72.43 (±50.41)	277319.44	1.50
			Nabumetone	710	0.25	93.37 (±51.33)	66294.12	0.36
			Naproxen	11673	4.09	56.79 (±57.37)	662898.03	3.58
			Phenylbutazone	130	0.05	20.75 (±11.0)	2697.26	0.01
			Piroxicam	16743	5.87	30.88 (±24.06)	516988.03	2.79
			Sulindac	139	0.05	132.36 (±53.83)	18398.35	0.10
			Tenoxicam	475	0.17	86.89 (±116.19)	41271.82	0.22
		4.1.2	Meloxicam	51994	18.22	62.64 (±37.84)	3257026.64	17.58
		4.1.3	Celecoxib	21897	7.67	211.89 (±79.24)	4639749.02	25.04
			Lumiracoxib	22773	7.98	129.75 (±77.16)	2954767.96	15.95
			Parecoxib	789	0.28	56.80 (±38.45)	44814.90	0.24
			Valdecoxib	1	0.00	0.01 (±)	0.01	0.00
	Total term 9			285334	29.90	64.94 (±71.24)	18528765.44	32.08
Total year 2006				954241	100.00	60.52 (±68.13)	57752267.02	100.00

Table B.2.2 The top twenty medicine items (all items) for 2005 – Database M

TOP 20 MEDICINE ITEMS ACCORDING TO COST 2005						
Number	**Trade name**	**Frequency (n)**	**Total cost per medicine item (R)**	**Frequency percentage (%)**	**Cost percentage (%)**	**Cost prevalence index**
1	Lipitor® 10mg tab	166536	31451055.35	0.84	1.66	1.98
2	Lipitor® 20mg tab	70987	19126984.68	0.36	1.01	2.83
3	Fosamax® 70mg tab	51797	17430911.77	0.26	0.92	3.53
4	Celebrex® 200mg	67993	15183633.29	0.34	0.80	2.34
5	Prexum® 4mg tab	98180	12654205.83	0.49	0.67	1.35
6	Adco-simvastatin® 20mg	112239	12594720.30	0.57	0.67	1.18
7	Coversyl® Plus	68268	12363387.59	0.34	0.65	1.90
8	Nexiam 40mg	42225	12320836.72	0.21	0.65	3.06
9	Cipralex 10mg	48512	12240924.47	0.24	0.65	2.65
10	Myprodol cap	183299	11061813.32	0.92	0.58	0.63
11	Premarin 0.625mg tab	107045	10471615.49	0.54	0.55	1.03
12	Aropax 20mg tab	37816	10194183.86	0.19	0.54	2.83
13	Seretide 50/250 accuhaler	27567	10141795.41	0.14	0.54	3.86
14	Eltroxin 100mcg tab	247943	10060238.72	1.25	0.53	0.43
15	Klacid XL 500mg tab	59843	9767900.77	0.30	0.52	1.71
16	Synap forte	80049	9288151.75	0.40	0.49	1.22
17	Cilift 20mg tab	74007	9052459.73	0.37	0.48	1.28
18	Avelon 400mg tab	43071	8475199.73	0.22	0.45	2.06
19	Plavix 75mg filmcoat tab	20899	8323378.10	0.11	0.44	4.18
20	Livifem 2.5mg tab	32440	8183197.91	0.16	0.43	2.65

* tab = refers to tablets
cap = refers to capsules
inj = refers to injections

Table B.2.3 The top twenty medicine items (all items) for 2006 – Database M

TOP 20 MEDICINE ITEMS ACCORDING TO COST 2006						
Number	**Trade name**	**Frequency (n)**	**Total cost per medicine item (R)**	**Frequency percentage (%)**	**Cost percentage (%)**	**Cost prevalence index**
1	Lipitor® 10mg tab	160500	30440185.64	0.75	1.49	1.99
2	Lipitor® 20mg tab	75542	20436897.83	0.35	1.00	2.84
3	Prexum® 4mg tab	131136	16875170.18	0.61	0.82	1.35
4	Cipralex® 10mg	65883	16651805.26	0.31	0.81	2.65
5	Fosamax® 70mg tab	45885	15360158.66	0.21	0.75	3.51
6	Nexiam® 40mg	50276	15089447.46	0.23	0.74	3.15
7	Adco-simvastatin® 20mg	130043	14384455.12	0.61	0.70	1.16
8	Celebrex® 200mg	64298	14185040.79	0.30	0.69	2.31
9	Stocrin® 600mg tab	53109	11542031.56	0.25	0.56	2.28
10	Synap® forte	98640	11427845.41	0.46	0.56	1.22
11	Herceptin®	1609	11365564.90	0.01	0.56	74.10
12	Plavix® 75mg filmcoat tab	27248	10741777.94	0.13	0.52	4.14
13	Eltroxin® 100mcg tab	264536	10444441.76	1.23	0.51	0.41
14	Aspen lamzid® tab	31501	10354031.53	0.15	0.51	3.45
15	In Novomix® 30 Flexpen 3ml	18684	10352796.98	0.09	0.51	5.81
16	Avelon® 400mg tab	51999	10152044.69	0.24	0.50	2.05
17	Klacid® XL 500mg tab	59849	9684590.57	0.28	0.47	1.70
18	Seretide® 50/250 accuhaler	31872	9638955.77	0.15	0.47	3.17
19	Premarin® 0.625mg tab	97313	9428394.11	0.45	0.46	1.02
20	Tavanic® 500mg	40619	8740791.81	0.19	0.43	2.26

* tab = refers to tablets
cap = refers to capsules
inj = refers to injections

APPENDIX C

Table C.1.1 Single NSAID therapy according to trade name for 2005 – Database M

Single NSAID-therapy 2005 - Database M						
Single Therapy 2005 (Trade name)	**Prevalence (n)**	**Prevalence percentage (%)**	**Average cost (R)**	**Total cost (R)**	**Cost percent-age (%)**	**Cost prevalence index**
A-Lennon diclofenac® 100mg supp	1054	0.11	55.76 (±34.06)	58771.97	0.10	0.88
A-Lennon diclofenac® 25mg tab	730	0.08	2.98 (±1.83)	2174.37	0.00	0.05
A-Lennon diclofenac® 50mg tab	1756	0.19	4.49 (±2.78)	7881.84	0.01	0.07
Adco-diclofenac® 75mg	607	0.07	3.54 (±5.33)	2150.54	0.00	0.06
Adco-diclofenac 50mg tab	25358	2.75	9.77 (±5.57)	247665.87	0.42	0.15
Adco-diclofenac® 100mg cap	46	0.00	113.96 (±65.49)	5241.99	0.01	1.80
Adco-diclofenac® 25mg tab	7077	0.77	6.41 (±4.87)	45377.56	0.08	0.10
Adco-diclofenac® 75mg/3ml inj	20221	2.19	3.72 (±4.56)	75271.30	0.13	0.06
Adco-ibuprofen® 400mg tab	6961	0.76	9.34 (±6.42)	65045.98	0.11	0.15
Adco-indomethacin® 25mg cap	1705	0.18	4.93 (±3.97)	8409.26	0.01	0.08
Adco-naproxen® 250mg tab	3660	0.40	27.61 (±14.65)	101044.74	0.17	0.44
Adco-piroxicam® 10mg cap	406	0.04	18.44 (±11.25)	7486.13	0.01	0.29
Adco-piroxicam® 20mg cap	3289	0.36	39.23 (±12.63)	129041.25	0.22	0.62
Adco-sulindac® 200mg tab	982	0.11	134.43 (±52.36)	132011.90	0.23	2.13
Aflamin® 25mg cap	451	0.05	4.33 (±4.26)	1956.76	0.00	0.07
Aleve® 220mg	2966	0.32	29.05 (±10.91)	86089.23	0.15	0.46
Amdocin® 25mg	1358	0.15	2.30 (±1.41)	3129.32	0.01	0.04
Apo-diclofenac® 100mg tab	120	0.01	91.94 (±39.72)	11032.51	0.02	1.45
Arcafenac® 75mg/3ml inj	2639	0.29	2.53 (±5.63)	6675.14	0.01	0.04
Arthrexin® 25mg cap	9790	1.06	9.85 (±6.66)	96436.62	0.17	0.16
Arthrexin® 50mg cap	2669	0.29	31.25 (±18.74)	83399.82	0.14	0.49
Arthrexin® 100mg supp	8347	0.91	85.30 (±52.27)	712017.69	1.22	1.35

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Arthrotec® 75mg tab	13756	1.49	133.02 (±56.39)	1829860.35	3.14	2.10
Arthrotec® tab	13829	1.50	134.40 (±58.37)	1858582.08	3.19	2.13
Austell-diclofenac® sod inj	8	0.00	6.53 (±5.75)	52.23	0.00	0.10
Be-tabs diclofenac® 3ml inj	1185	0.13	7.79 (±2.67)	9236.71	0.02	0.12
Be-tabs naproxen® 250mg	101	0.01	11.64 (±7.87)	1175.57	0.00	0.18
Be-tabs naproxen® 500mg	8	0.00	38.20 (±23.99)	305.58	0.00	0.60
Betacin® 25mg cap	6931	0.75	2.64 (±2.58)	18301.82	0.03	0.04
Betagesic® 200mg tab	1439	0.16	20.36 (±8.10)	29296.89	0.05	0.32
Betaprofen® 200mg tab	5946	0.64	2.53 (±1.72)	15042.55	0.03	0.04
Betaprofen® 400mg FC	1993	0.22	4.60 (±3.64)	9166.25	0.02	0.07
Bextra® 40	11316	1.23	126.92 (±87.12)	1436190.21	2.46	2.01
Brexecam® 20mg tab	11485	1.25	68.81 (±29.14)	790334.87	1.36	1.09
Brufen® 200mg tab	6146	0.67	14.87 (±12.31)	91378.11	0.16	0.24
Brufen® 400mg tab	15100	1.64	25.07 (±11.21)	378507.95	0.65	0.40
Brufen® 600mg tab	3336	0.36	52.01 (±30.89)	173499.30	0.30	0.82
Brufen® paed susp	4131	0.45	44.32 (±19.71)	183068.29	0.31	0.70
Brufen® retard 800mg tab	2729	0.30	160.09 (±72.55)	436875.60	0.75	2.53
Cataflam® 50mg tab	4722	0.51	99.53 (±37.25)	469979.09	0.81	1.57
Cataflam® D 50mg disp tab	66877	7.25	83.65 (±35.33)	5594482.98	9.60	1.32
Celebrex® 100mg cap	10060	1.09	156.32 (±70.23)	1572572.00	2.70	2.47
Celebrex® 200mg cap	67993	7.38	223.31 (±72.19)	15183633.29	26.05	3.53
Clinoril® 200mg tab	1	0.00	77.18 (±)	77.18	0.00	1.22
Coxflam® 15mg tab	69317	7.52	74.42 (±29.20)	5158351.33	8.85	1.18
Coxflam® 7.5mg tab	52745	5.72	36.63 (±13.65)	1932241.28	3.31	0.58
CPL ALNC piroxicam® 20mg	111	0.01	13.18 (±7.38)	1463.06	0.00	0.21
Dicloflam® blackcurrent	10285	1.12	53.82 (±22.28)	553592.92	0.95	0.85

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Diclohexal® 25mg	2548	0.28	4.27 (±3.66)	10895.24	0.02	0.07
Diclohexal® 100mg supp	1625	0.18	80.44 (±55.08)	130720.59	0.22	1.27
Diclohexal® 50mg	12245	1.33	13.88 (±6.96)	170030.15	0.29	0.22
Diclohexal® K 50mg tab	43	0.00	47.08 (±11.00)	2024.27	0.00	0.74
Difenject® 3ml inj	2150	0.23	1.96 (±2.23)	4211.96	0.01	0.03
Dynak® 50mg	53	0.01	45.49 (±10.82)	2410.92	0.00	0.72
Dynofen® 200mg	2	0.00	5.05 (±0.25)	10.11	0.00	0.08
Feldene® 10mg cap	6	0.00	136.50 (±31.63)	819.02	0.00	2.16
Feldene® 20mg cap	102	0.01	131.25 (±51.43)	13387.81	0.02	2.08
Feldene® 20mg supp	6	0.00	89.68 (±33.46)	538.08	0.00	1.42
Feldene® disp 20mg tab	132	0.01	123.91 (±53.37)	16356.34	0.03	1.96
Feldene® IM 20mg/ml inj	43	0.00	18.66 (±9.01)	802.27	0.00	0.30
Flamaret® 25mg cap	3	0.00	7.41 (±1.97)	22.24	0.00	0.12
Flamecid® 25mg cap	200	0.02	5.22 (±3.02)	1043.38	0.00	0.08
Flexocam® 15mg tab	1105	0.12	69.14 (±27.72)	76396.31	0.13	1.09
Flexocam® 7.5mg tab	540	0.06	32.02 (±14.24)	17290.89	0.03	0.51
Fortfe®n 3ml inj	6228	0.68	2.80 (±3.74)	17447.57	0.03	0.04
Fortfen® SR 100mg cap	8795	0.95	66.70 (±20.54)	586637.96	1.01	1.05
Froben® 100mg tab	2	0.00	89.41 (±22.46)	178.82	0.00	1.41
Gulf Indomethacin® 25mg	184	0.02	2.85 (±1.83)	525.31	0.00	0.05
Iboflam® 200mg tab	284	0.03	4.75 (±2.49)	1349.07	0.00	0.08
Ibugesic® 100mg/5ml susp	47	0.01	25.45 (±4.52)	1196.21	0.00	0.40
Ibumed® 200mg tab	157	0.02	14.27 (±4.75)	2241.06	0.00	0.23
Ibumed® SR 300mg tab	8	0.00	16.53 (±7.59)	132.28	0.00	0.26
Ibunate® 200mg	420	0.05	2.15 (±0.96)	902.01	0.00	0.03

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Indocid® 100mg supp	1398	0.15	126.21 (±66.52)	176443.81	0.30	2.00
Indocid® R 75mg cap	218	0.02	89.44 (±44.83)	19497.75	0.03	1.41
Inflaban® SR 100mg	21	0.00	192.06 (±78.72)	4033.23	0.01	3.04
Inflazone® 100mg tab	136	0.01	14.28 (±7.79)	1941.76	0.00	0.23
Inflazone® 200mg tab	317	0.03	23.65 (±10.78)	7497.28	0.01	0.37
Inza® 200mg tab	8353	0.91	7.30 (±4.99)	60973.03	0.10	0.12
Inza® 400mg tab	21225	2.30	17.80 (±12.55)	377911.09	0.65	0.28
K-Fenak® 50mg tab	4778	0.52	50.51 (±17.59)	241352.72	0.41	0.80
Ketoflam® 200mg cap	6790	0.74	76.97 (±16.84)	522608.80	0.90	1.22
Lenafen® 200mg	154	0.02	14.29 (±5.85)	2200.73	0.00	0.23
Loxiflam® 15mg	14728	1.60	82.90 (±25.04)	1220946.14	2.09	1.31
Loxiflam® 7.5mg	14031	1.52	41.06 (±15.43)	576094.10	0.99	0.65
Meclomen® 100mg cap	4	0.00	85.35 (±62.62)	341.40	0.00	1.35
Mediflex® 25mg cap	167	0.02	6.08 (±4.20)	1016.12	0.00	0.10
Melflam® 15mg tab	12	0.00	56.39 (±30.26)	676.64	0.00	0.89
Melflam® 7.5mg tab	10	0.00	26.27 (±11.57)	626.75	0.00	0.99
Merck-diclofenac® 50mg tab	11285	1.22	6.57 (±4.81)	74197.27	0.13	0.10
Merck-diclofenac® 25mg tab	2642	0.29	2.98 (±2.58)	7863.16	0.01	0.05
Merck-naproxen® tab	1723	0.19	13.90 (±11.54)	23955.93	0.04	0.22
Merck-piroxicam® 10mg	71	0.01	13.78 (±5.58)	978.16	0.00	0.22
Merck-piroxicam® 20mg	63	0.01	18.63 (±6.62)	1173.70	0.00	0.29
Methocaps® 25mg	31	0.00	8.57 (±5.02)	264.65	0.00	0.14
Micro diclofenac® 75mg/3ml	8250	0.89	3.07 (±7.60)	25316.83	0.04	0.05
Mobic® 15mg supp	564	0.06	201.96 (±103.79)	113908.50	0.20	3.19
Mobic® 15mg tab	1888	0.20	176.35 (±76.04)	332955.13	0.57	2.79

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Mobic® 15mg/1.5ml inj	5372	0.58	9.19 (±7.87)	49397.13	0.08	0.15
Mobic® 7.5mg tab	2403	0.26	143.65 (±55.66)	345201.37	0.59	2.27
Myproflam® 200mg cap	1487	0.16	75.10 (±16.37	111672.81	0.19	1.19
Nafasol® 500mg supp	199	0.02	105.33 (±58.33)	20961.10	0.04	1.67
Nafasol® EC 250mg tab	8477	0.92	61.96 (±36.78)	525225.21	0.90	0.98
Nafasol® EC 500mg tab	6587	0.71	107.61 (±57.05)	708813.34	1.22	1.70
Napflam® 250mg tab	2097	0.23	19.01 (±11.43)	39860.39	0.07	0.30
Napflam® 500mg tab	3080	0.33	35.95 (±18.12)	110736.32	0.19	0.57
Naprel® 250mg tab	18	0.00	25.15 (±10.75)	452.65	0.00	0.40
Naproscript® 250mg tab	443	0.05	8.43 (±5.55)	3732.90	0.01	0.13
Naproscript® 500mg tab	1350	0.15	21.68 (±9.09)	29266.38	0.05	0.34
Naprosyn® 250mg tab	594	0.06	78.46 (±30.58)	46603.58	0.08	1.24
Naprosyn® 500mg tab	117	0.01	124.10 (±75.44)	14519.56	0.02	1.96
Naprosyn® EC 250mg tab	158	0.02	142.39 (±46.63)	22497.08	0.04	2.25
Naprosyn® EC 500mg tab	126	0.01	240.29 (±120.54)	30276.32	0.05	3.80
Naprosyn® SR 500mg tab	21	0.00	249.75 (±105.48)	5244.67	0.01	3.95
NISAID® 25mg cap	314	0.03	10.75 (±4.40)	3376.98	0.01	0.17
Norflam® T 200mg	21	0.00	14.89 (±5.74)	312.77	0.00	0.24
Orucote® 100mg tab	4	0.00	152.98 (±6.58)	611.92	0.00	2.42
Oruject® 100mg/2ml inj	1	0.00	18.00 (±)	18.00	0.00	0.28
Oruvail® 200mg cap	389	0.04	198.60 (±60.30)	77254.05	0.13	3.14
Panamor® 100mg supp	5186	0.56	86.12 (±58.02)	446604.37	0.77	1.36
Panamor® 12.5mg supp	3090	0.34	24.31 (±11.13)	75105.84	0.13	0.38
Panamor® 25mg supp	1577	0.17	63.49 (±40.15)	100123.16	0.17	1.00
Panamor® 25mg tab	3625	0.39	18.19 (±12.98)	65952.53	0.11	0.29

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Panamor® 75mg/3ml inj	7042	0.76	4.58 (±6.36)	32259.22	0.06	0.07
Panamor® AT 50mg tab	19882	2.16	12.11 (±8.48)	240794.38	0.41	0.19
Panamor SR 100mg tab	8413	0.91	74.48 (±20.91)	626639.35	1.08	1.18
Panamor® SR 75mg tab	3996	0.43	87.10 (±39.71)	348057.66	0.60	1.38
Pharmflam® 100mg supp	1	0.00	62.36 (±)	62.36	0.00	0.99
Pharmflam® 25mg tab	91	0.01	18.29 (±8.05)	1664.87	0.00	0.29
Pixicam® 20mg disp tab	9796	1.06	24.00 (±6.97)	235155.76	0.40	0.38
Pyrocaps® 20mg cap	17285	1.88	17.96 (±6.53)	310193.13	0.53	0.28
Ranfen® 200mg tab	3700	0.40	2.32 (±1.58)	8581.02	0.01	0.04
Ranfen® 400mg tab	2679	0.29	4.61 (±2.95)	12362.02	0.02	0.07
Rayzon® IV-IM powder + 2ml NaCl	1874	0.20	69.46 (±43.43)	130166.51	0.22	1.10
Relifen® 500mg tab	145	0.02	158.16 (±73.18)	22933.33	0.04	2.50
Relisan® 500mg tab	996	0.11	83.09 (±32.77)	82759.17	0.14	1.31
Relitone® 500mg tab	884	0.10	109.85 (±42.14)	97108.80	0.17	1.74
Restameth-SR® 75mg	58	0.01	47.05 (±18.41)	2728.89	0.00	0.74
Rheugesic® DI 20mg tab	5900	0.64	42.04 (±14.56)	248043.94	0.43	0.66
Rolab-antiflam® 200mg	4	0.00	10.31 (±3.89)	41.26	0.00	0.16
Rolab-piroxicam® 10mg	88	0.01	16.27 (±7.44)	1431.98	0.00	0.26
Rolab-piroxicam® 20mg	1002	0.11	23.44 (±9.14)	23491.96	0.04	0.37
Roxifen® 20mg cap	619	0.07	16.12 (±5.69)	9979.60	0.02	0.25
Sandoz Diclofenac® 100SR	13386	1.45	50.72 (±13.75)	678922.08	1.16	0.80
Sandoz Diclofenac® 25	2843	0.31	10.99 (±10.61)	31238.77	0.05	0.17
Sandoz Diclofenac® 50	12576	1.36	12.90 (±7.58)	162294.09	0.28	0.20
Sandoz Ibuprofen® 200mg tab	1268	0.14	7.62 (±5.24)	9666.90	0.02	0.12
Sandoz Ibuprofen® 400mg tab	4073	0.44	12.98 (±10.17)	52891.40	0.09	0.21

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Sandoz Ibuprofen® 600mg tab	3239	0.35	55.57 (±33.67)	179998.44	0.31	0.88
Sandoz Indomethacin® 25mg	770	0.08	14.90 (±11.80)	11471.09	0.02	0.24
Sandoz Indomethacin® LA 75	1521	0.16	74.25 (±24.50)	112931.62	0.19	1.17
Sandoz Meloxicam® 7.5mg tab	129	0.01	34.47 (±12.45)	4446.08	0.01	0.55
Sandoz Meloxicam® 15mg tab	197	0.02	67.44 (28.63)	13285.90	0.02	1.07
Sandoz Naproxen® 250mg	1194	0.13	37.74 (±20.96)	45065.96	0.08	0.60
Sandoz Naproxen® 500mg	1429	0.16	44.90 (±28.58)	64158.40	0.11	0.71
Sandoz Piroxicam® disp 20	4388	0.48	23.06 (±9.19)	101212.90	0.17	0.36
Synflex® 275mg tab	6485	0.70	125.41 (±45.61)	813281.29	1.40	1.98
Synflex® 550mg tab	1201	0.13	218.66 (±102.29)	262608.62	0.45	3.46
Tilcotil® 20mg inj	1226	0.13	32.47 (±20.57)	39809.99	0.07	0.51
Tilcotil® 20mg supp	26	0.00	240.51 (±181.03)	6253.32	0.01	3.80
Tilcotil® 20mg tab	380	0.04	262.69 (±103.22)	99822.66	0.17	4.15
Tilcotil® disp 20mg	19	0.00	225.54 (±125.38)	4285.26	0.01	3.57
Tobitil® 20mg	137	0.01	107.93 (±31.98)	14785.91	0.03	1.71
Trio-diclofenac® 3ml	1315	0.14	7.83 (±3.88)	10291.11	0.02	0.12
Veltex® 100mg caps	6633	0.72	144.61 (±57.01)	959178.98	1.65	2.29
Veltex® 75mg caps	12274	1.33	72.76 (±40.92)	893036.99	1.53	1.15
Vioxx® 12.5mg	1	0.00	0.01 (±)	0.01	0.00	0.00
Vioxx® 25mg	20	0.00	151.11 (±129.24)	3022.15	0.01	2.39
Voltaren® drops	410	0.04	81.05 (±21.19)	33231.57	0.06	1.28
Voltaren® 100mg supp	6946	0.75	89.90 (±62.15)	624428.67	1.07	1.42
Voltaren® 12.5mg supp	4703	0.51	26.87 (±12.59)	126366.23	0.22	0.42
Voltaren® 25mg supp	2269	0.25	62.07 (±39.99)	140832.73	0.24	0.98
Voltaren® 25mg tbec	3102	0.34	25.53 (±15.81)	79200.65	0.14	0.40

Table C.1.1 (continue)

Single Therapy 2005 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent-age (%)	Cost prevalence index
Voltaren® 75mg tbcr	3359	0.36	108.98 (±49.54)	366066.89	0.63	1.72
Voltaren® 75mg/3ml inj	34292	3.72	10.33 (±7.87)	354277.72	0.61	0.16
Voltaren® acti-go tab	1285	0.14	39.50 (±11.38)	50757.72	0.09	0.62
Voltaren® GT 50mg tbec	9925	1.08	45.10 (±23.30)	447586.75	0.77	0.71
Voltaren® SR 100mg tbcr	2870	0.31	119.12 (±44.19)	341865.56	0.59	1.88
Xefo® 4mg	947	0.10	64.21 (±35.54)	60805.26	0.10	1.02
Xefo® 8 IV/IM 2ml	3924	0.43	26.55 (±13.23)	104169.50	0.18	0.42
Xefo® 8mg	11404	1.24	91.27 (±49.05)	1040876.44	1.79	1.44
Xycam® 20mg cap	5380	0.58	22.37 (±7.45)	120335.21	0.21	0.35
Xycam® 20mg supp	15	0.00	185.35 (±118.46)	2780.27	0.00	2.93
Xycam® disp 20mg	3590	0.39	24.23 (±8.84)	86981.75	0.15	0.38
Zydus-meloxicam® 7.5mg tab	2	0.00	27.12 (±)	54.24	0.00	0.43
TOTAL	**921863**	**100.00**	**63.23 (±69.80)**	**58290412.55**	**100.00**	**1.00**

Table C.1.2 Single NSAID therapy according to trade name for 2006 – Database M

Single NSAID-therapy 2006 - Database M						
Single Therapy 2006 (Trade name)	**Prevalence (n)**	**Prevalence percentage (%)**	**Average cost (R)**	**Total cost (R)**	**Cost percent -age (%)**	**Cost prevalence index**
A-Lennon diclofenac® 100mg supp	929	0.10	51.78 (±28.99)	48106.84	0.08	0.86
A-Lennon diclofenac® 25mg tab	774	0.08	2.87 (±1.57)	2225.66	0.00	0.05
A-Lennon diclofenac® 50mg tab	1547	0.16	4.31 (±2.78)	6671.46	0.01	0.07
Acu-diclofenac® 75mg	364	0.04	3.75 (±6.32)	1364.02	0.00	0.06
Adco-clofelam® 50mg tab	275	0.03	40.93 (±17.79)	11255.87	0.02	0.68
Adco-diclofenac® 50mg tab	22368	2.34	9.23 (±5.92)	206480.40	0.36	0.15
Adco-diclofenac® 100mg cap	124	0.01	93.45 (±37.10)	11588.46	0.02	1.54
Adco-diclofenac® 25mg tab	7880	0.83	5.40 (±4.81)	42529.86	0.07	0.09
Adco-diclofenac® 75mg/3ml inj	22250	2.33	3.00 (±3.99)	66862.52	0.12	0.05
Adco-ibuprofen® 400mg tab	7289	0.76	8.79 (±6.29)	64108.33	0.11	0.15
Adco-indomethacin® 25mg cap	1703	0.18	4.10 (±3.73)	6986.18	0.01	0.07
Adco-meloxicam 15mg tab®	425	0.04	54.75 (±31.07)	23270.39	0.04	0.90
Adco-meloxicam 7.5mg tab®	301	0.03	31.40 (±11.50)	9451.49	0.02	0.52
Adco-naproxen® 250mg tab	4051	0.42	25.10 (±15.81)	101671.80	0.18	0.41
Adco-piroxicam® 10mg cap	307	0.03	19.27 (±13.46)	5914.86	0.01	0.32
Adco-piroxicam® 20mg cap	2405	0.25	38.53 (±13.38)	92674.56	0.16	0.64
Adco-sulindac® 200mg tab	460	0.05	135.32 (±54.31)	62246.26	0.11	2.24
Aflamin® 25mg cap	403	0.04	4.07 (±4.19)	1641.86	0.00	0.07
Aleve® 220mg	3215	0.34	27.46 (±10.61)	88276.50	0.15	0.45
Amdocin® 25mg	1130	0.12	2.14 (±1.98)	2418.28	0.00	0.04
Apo-diclofenac® 100mg tab	19	0.00	82.27 (±)	1563.13	0.00	1.36
Arcafenac® 75mg/3ml inj	2954	0.31	2.62 (±7.31)	7739.65	0.01	0.04
Arthrexin® 25mg cap	9651	1.01	9.24 (±6.41)	89185.97	0.15	0.15
Arthrexin® 50mg cap	2455	0.26	33.06 (±20.09)	81160.86	0.14	0.55
Arthrexin® 100mg supp	8824	0.92	83.18 (±52.35)	733946.04	1.27	1.37

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Arthrotec® 75mg tab	13514	1.42	133.64 (±57.09)	1806040.73	3.13	2.21
Arthrotec® tab	12418	1.30	135.10 (±58.95)	1677700.18	2.90	2.23
Aspen naproxen® 275mg tab	1013	0.11	85.26 (±36.16)	86370.69	0.15	1.41
Austell-diclofenac® sod inj	234	0.02	3.38 (±4.88)	791.07	0.00	0.06
Be-tabs diclofenac® 3ml inj	603	0.06	2.82 (±3.32)	1698.64	0.00	0.05
Be-tabs naproxen® 250mg	491	0.05	10.81 (±8.44)	5308.48	0.01	0.18
Be-tabs naproxen® 500mg	36	0.00	64.40 (±47.02)	2318.42	0.00	1.06
Betacin® 25mg cap	10049	1.05	2.05 (±2.25)	20650.66	0.04	0.03
Betagesic® 200mg tab	1717	0.18	18.57 (±7.54)	31880.21	0.06	0.31
Betaprofen® 200mg tab	6359	0.67	2.26 (±1.89)	14343.86	0.02	0.04
Betaprofen® 400mg FC	3379	0.35	4.29 (±3.41)	14508.90	0.03	0.07
Bextra® 40	8	0.00	0.02 (±0.02)	0.15	0.00	0.00
Brexecam® 20mg tab	11158	1.17	67.60 (±30.55)	754343.26	1.31	1.12
Brufen® 200mg tab	6927	0.73	12.13 (±11.84)	84012.69	0.15	0.20
Brufen® 400mg tab	16664	1.75	24.27 (±12.64)	404425.58	0.70	0.40
Brufen® 600mg tab	3448	0.36	51.67 (±29.43)	178174.84	0.31	0.85
Brufen® paed susp	3403	0.36	41.53 (±18.27)	141325.75	0.24	0.69
Brufen® retard 800mg tab	2373	0.25	161.16 (±74.56)	382423.31	0.66	2.66
Cataflam® 50mg tab	585	0.06	91.48 (±42.52)	53517.20	0.09	1.51
Cataflam® D 50mg disp tab	50426	5.28	66.40 (±31.34)	3348145.62	5.80	1.10
Celebrex® 100mg cap	10430	1.09	149.63 (±69.99)	1560625.85	2.70	2.47
Celebrex® 200mg cap	64298	6.74	220.61 (±74.82)	14185040.79	24.56	3.65
Coxflam® 15mg tab	76120	7.98	78.27 (±28.40)	5957966.55	10.32	1.29
Coxflam® 7.5mg tab	48907	5.13	36.83 (±14.47)	1801148.92	3.12	0.61
CPL ALNC piroxicam® 20mg	35	0.00	9.46 (±4.95)	331.03	0.00	0.16
Dicloflam® 50mg dispers tab	471	0.05	52.16 (±25.85)	24567.82	0.04	0.86
Dicloflam® blackcurrent	42248	4.43	52.57 (±23.81)	2221072.71	3.85	0.87

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Diclohexal® 25mg	3238	0.34	3.63 (±3.36)	11769.71	0.02	0.06
Diclohexal® 100mg supp	1819	0.19	80.22 (±46.97)	145925.32	0.25	1.33
Diclohexal® 50mg	10810	1.13	13.49 (±7.58)	145831.43	0.25	0.22
Diclohexal® K 50mg tab	1169	0.12	47.11 (±19.28)	55071.59	0.10	0.78
Difen® SR 100mg	23	0.00	57.32 (±20.03)	1318.32	0.00	0.95
Difenject® 3ml inj	2596	0.27	1.33 (±2.91)	3458.34	0.01	0.02
Dynak® 50mg	1178	0.12	46.91 (±18.10)	55264.94	0.10	0.78
Dynofen® 200mg	5	0.00	3.09 (±0.89)	15.44	0.00	0.05
Fametacin® 25mg cap	2	0.00	4.50 (±)	9.00	0.00	0.07
Flamecid® 25mg cap	164	0.02	4.31 (±2.71)	707.73	0.00	0.07
Flexocam® 15mg tab	4762	0.50	71.38 (±28.11)	339905.13	0.59	1.18
Flexocam® 7.5mg tab	2508	0.26	31.21 (±13.54)	78284.75	0.14	0.52
Fortfe®n 3ml inj	4923	0.52	1.89 (±2.49)	9315.53	0.02	0.03
Fortfen® SR 100mg cap	8070	0.85	67.17 (±19.18)	542050.10	0.94	1.11
Gulf Indomethacin® 25mg	306	0.03	2.99 (±1.62)	914.15	0.00	0.05
Iboflam® 200mg tab	403	0.04	5.67 (±2.22)	2284.58	0.00	0.09
Ibugesic® 100mg/5ml susp	1668	0.17	25.25 (±7.76)	42117.37	0.07	0.42
Ibumed® 200mg tab	50	0.01	11.02 (±6.64)	551.26	0.00	0.18
Ibumed® SR 300mg tab	7	0.00	20.96 (±12.29)	146.75	0.00	0.35
Ibunate® 200mg	522	0.05	2.05 (±0.95)	1070.11	0.00	0.03
Indocid® 100mg supp	1252	0.13	132.41 (±65.93)	165773.69	0.29	2.19
Inflazone® 100mg tab	114	0.01	16.19 (±8.97)	1845.70	0.00	0.27
Inflazone® 200mg tab	412	0.04	23.35 (±11.21)	9621.13	0.02	0.39
Inza® 200mg tab	7212	0.76	6.71 (±5.01)	48384.77	0.08	0.11
Inza® 400mg tab	17117	1.79	17.47 (±13.58)	299113.32	0.52	0.29
K-Fenak® 50mg tab	9845	1.03	47.55 (±21.58)	468123.44	0.81	0.79
Ketoflam® 200mg cap	5750	0.60	75.60 (±18.27)	434682.20	0.75	1.25

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Lenafen® 200mg	213	0.02	13.94 (±5.60)	2970.37	0.01	0.23
Loxiflam® 15mg	15241	1.60	80.51 (±25.78)	1227084.10	2.12	1.33
Loxiflam® 7.5mg	11352	1.19	38.67 (±15.41)	439000.60	0.76	0.64
M-Cam® 7.5mg tab	91	0.01	52.50 (±28.54)	4777.20	0.01	0.87
M-Cam® 15mg tab	121	0.01	26.19 (±10.37)	3169.66	0.01	0.43
Meclomen® 100mg cap	2	0.00	87.39 (±7.56)	174.79	0.00	1.44
Mediflex® 25mg cap	126	0.01	7.79 (±5.38)	981.14	0.00	0.13
Melflam® 15mg tab	630	0.07	59.11 (±31.50)	37241.28	0.06	0.98
Melflam® 7.5mg tab	438	0.05	31.41 (±12.86)	13757.49	0.02	0.52
Merck-diclofenac® 50mg tab	15333	1.61	6.30 (±5.67)	96572.93	0.17	0.10
Merck-diclofenac® 25mg tab	3486	0.37	2.58 (±2.67)	8999.16	0.02	0.04
Merck-naproxen® tab	2063	0.22	12.39 (±8.94)	25567.79	0.04	0.20
Merck-piroxicam® 20mg	8	0.00	19.41 (±2.55)	155.32	0.00	0.32
Methocaps® 25mg	5	0.00	6.77 (±6.65)	33.85	0.00	0.11
Micro diclofenac® 75mg/3ml	8847	0.93	1.99 (±6.40)	17626.48	0.03	0.03
Micro diclofenac multidose	4	0.00	8.02 (±1.23)	32.07	0.00	0.13
Mobic® 15mg supp	621	0.07	236.18 (±119.48)	146667.87	0.25	3.90
Mobic® 15mg tab	1250	0.13	179.69 (±80.35)	224608.32	0.39	2.97
Mobic® 15mg/1.5ml inj	5106	0.54	8.51 (±7.21)	43477.62	0.08	0.14
Mobic® 7.5mg tab	1552	0.16	143.71 (±56.86)	223036.63	0.39	2.37
Myproflam® 200mg cap	186	0.02	95.04 (±17.09)	17676.91	0.03	1.57
Nafasol® 500mg supp	191	0.02	87.08 (±40.38)	16632.64	0.03	1.44
Nafasol® EC 250mg tab	6856	0.72	59.93 (±38.73)	410879.84	0.71	0.99
Nafasol® EC 500mg tab	5357	0.56	110.57 (±58.69)	592317.96	1.03	1.83
Napflam® 250mg tab	1869	0.20	18.00 (±11.24)	33640.51	0.06	0.30
Napflam® 500mg tab	3392	0.36	33.89 (±17.20)	114959.52	0.20	0.56
Naprel® 250mg tab	60	0.01	17.74 (±6.21)	1064.58	0.00	0.29

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Naproscript® 250mg tab	1113	0.12	9.06 (±5.97)	10088.18	0.02	0.15
Naproscript® 500mg tab	3506	0.37	19.88 (±7.49)	69686.32	0.12	0.33
Naprosyn® 250mg tab	253	0.03	78.00 (±25.28)	19733.37	0.03	1.29
Naprosyn® 500mg tab	43	0.00	128.39 (±48.69)	5521.02	0.01	2.12
Naprosyn® EC 250mg tab	40	0.00	144.89 (±61.47)	5795.68	0.01	2.39
Naprosyn® EC 500mg tab	73	0.01	189.07 (±131.78)	13801.88	0.02	3.12
Naprosyn® SR 500mg tab	6	0.00	231.22 (±28.88)	1387.32	0.00	3.82
NISAID® 25mg cap	668	0.07	11.06 (±4.37)	7389.65	0.01	0.18
Norflam® T 200mg	7	0.00	16.25 (±4.84)	113.78	0.00	0.27
Oruvail® 200mg cap	353	0.04	195.47 (±61.68)	69000.56	0.12	3.23
Panamor® 100mg supp	5754	0.60	83.90 (±59.59)	482737.59	0.84	1.39
Panamor® 12.5mg supp	3122	0.33	23.82 (±11.89)	74377.12	0.13	0.39
Panamor® 25mg supp	1612	0.17	59.81 (±42.14)	96411.43	0.17	0.99
Panamor® 25mg tab	3306	0.35	17.60 (±12.19)	58176.52	0.10	0.29
Panamor® 75mg/3ml inj	6729	0.71	4.03 (±5.84)	27144.03	0.05	0.07
Panamor® AT 50mg tab	16168	1.69	11.35 (±7.66)	183448.44	0.32	0.19
Panamor SR 100mg tab	8341	0.87	73.62 (±22.14)	614067.43	1.06	1.22
Panamor® SR 75mg tab	3490	0.37	88.85 (±43.87)	310092.49	0.54	1.47
Pharmflam® 25mg tab	2	0.00	20.14 (±5.69)	40.29	0.00	0.33
Pixicam® 20mg disp tab	8776	0.92	23.35 (±7.40)	204956.37	0.35	0.39
Prexige® 100mg tab	119729	12.55	189.26 (±65.71)	2219893.34	3.84	0.31
Prexige® 400mg tab	15371	1.61	82.38 (±45.66)	1266206.44	2.19	1.36
Pyrocaps® 20mg cap	19171	2.01	18.07 (±6.02)	346382.84	0.60	0.30
Ranfen® 200mg tab	4268	0.45	1.73 (±1.74)	7386.75	0.01	0.03
Ranfen® 400mg tab	4186	0.44	3.21 (±2.81)	13456.01	0.02	0.05
Rayzon® IV-IM powder + 2ml NaCl	2774	0.29	64.82 (±46.49)	179807.29	0.31	1.07
Relifen® 500mg tab	710	0.07	119.02 (±76.69)	84506.49	0.15	1.97

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Relisan® 500mg tab	1055	0.11	83.53 (±30.89)	88128.66	0.15	1.38
Relitone® 500mg tab	790	0.08	105.98 (±47.26)	83721.71	0.14	1.75
Restameth-SR® 75mg	16	0.00	54.08 (±29.80)	865.28	0.00	0.89
Rheugesic® DI 20mg tab	4814	0.50	40.61 (±12.69)	195482.39	0.34	0.67
Rolab-antiflam® 200mg	1	0.00	9.27 (±)	9.27	0.00	0.15
Rolab-piroxicam® 10mg	45	0.00	11.02 (±6.02)	496.07	0.00	0.18
Rolab-piroxicam® 20mg	290	0.03	20.76 (±7.69)	6019.69	0.01	0.34
Roxifen® 20mg cap	556	0.06	15.42 (±4.39)	8572.71	0.01	0.25
Sandoz Diclofenac® 100SR	12828	1.34	50.77 (±14.01)	651222.88	1.13	0.84
Sandoz Diclofenac® 25	2391	0.25	9.13 (±9.80)	21822.29	0.04	0.15
Sandoz Diclofenac® 50	11910	1.25	13.92 (±10.17)	165802.14	0.29	0.23
Sandoz Ibuprofen® 200mg tab	1312	0.14	6.68 (±5.28)	8760.62	0.02	0.11
Sandoz Ibuprofen® 400mg tab	4039	0.42	11.24 (±8.71)	45411.39	0.08	0.19
Sandoz Ibuprofen® 600mg tab	2701	0.28	56.53 (±35.53)	152689.98	0.26	0.93
Sandoz Indomethacin® 25mg	638	0.07	10.99 (±11.29)	7010.87	0.01	0.18
Sandoz Indomethacin® LA 75	1622	0.17	70.14 (±28.15)	113764.12	0.20	1.16
Sandoz Meloxicam® 7.5mg tab	1033	0.11	31.53 (±13.59)	32567.34	0.06	0.52
Sandoz Meloxicam® 15mg tab	2243	0.24	55.75 (±30.30)	125052.16	0.22	0.92
Sandoz Naproxen® 250mg	883	0.09	34.73 (±17.77)	30669.80	0.05	0.57
Sandoz Naproxen® 500mg	1038	0.11	36.25 (±21.07)	37632.05	0.07	0.60
Sandoz Piroxicam® disp 20	3037	0.32	23.94 (±10.83)	72703.97	0.13	0.40
Synflex® 275mg tab	5129	0.54	118.75 (±45.92)	609053.11	1.05	1.96
Synflex® 550mg tab	1182	0.12	182.05 (±96.12)	215183.18	0.37	3.01
Tilcotil® 20mg inj	1279	0.13	30.32 (±21.83)	38783.91	0.07	0.50
Tilcotil® 20mg supp	19	0.00	261.95 (±125.16)	4977.10	0.01	4.33
Tilcotil® 20mg tab	442	0.05	272.83 (±89.25)	120592.85	0.21	4.51

Table C.1.2 (continue)

Single Therapy 2006 (Trade name)	Prevalence (n)	Prevalence percentage (%)	Average cost (R)	Total cost (R)	Cost percent -age (%)	Cost prevalence index
Tilcotil® disp 20mg	23	0.00	295.16 (±103.82)	6788.68	0.01	4.88
Tobitil® 20mg	1	0.00	118.07 (±)	118.07	0.00	1.95
Trio-diclofenac® 3ml	968	0.10	7.59 (±3.59)	7352.13	0.01	0.13
Veltex® 100mg caps	6123	0.64	143.51 (±56.50)	878730.83	1.52	2.37
Veltex® 75mg caps	13431	1.41	73.36 (±41.75)	985319.94	1.71	1.21
Voltaren® drops	317	0.03	81.70 (±34.24)	25898.97	0.04	1.35
Voltaren® 100mg supp	6801	0.71	79.56 (±55.13)	541070.55	0.94	1.31
Voltaren® 12.5mg supp	4344	0.46	25.43 (±13.44)	110473.33	0.19	0.42
Voltaren® 25mg supp	2043	0.21	62.73 (±74.04)	128160.71	0.22	1.04
Voltaren® 25mg tbec	2211	0.23	24.06 (±15.21)	53205.93	0.09	0.40
Voltaren® 75mg tbcr	2947	0.31	104.82 (±50.94)	308920.78	0.53	1.73
Voltaren® 75mg/3ml inj	34196	3.58	9.59 (±7.72)	328115.21	0.57	0.16
Voltaren® acti-go tab	3095	0.32	37.79 (±13.74)	116975.24	0.20	0.62
Voltaren® GT 50mg tbec	8806	0.92	42.36 (±22.89)	373049.17	0.65	0.70
Voltaren® SR 100mg tbcr	2644	0.28	118.00 (±45.98)	311986.68	0.54	1.95
Xefo® 4mg	883	0.09	65.59 (±34.98)	57916.03	0.10	1.08
Xefo® 8 IV/IM 2ml	2829	0.30	23.99 (±12.72)	67874.92	0.12	0.40
Xefo® 8mg	10065	1.05	90.92 (±49.07)	915124.23	1.58	1.50
Xycam® 20mg cap	5526	0.58	21.41 (±6.95)	118317.80	0.20	0.35
Xycam® 20mg supp	5	0.00	211.83 (±130.03)	1059.13	0.00	3.50
Xycam® disp 20mg	3739	0.39	24.48 (±8.73)	91539.75	0.16	0.40
Zydus-meloxicam® 15mg tab	354	0.04	40.28 (±24.08)	14259.33	0.02	0.67
Zydus-meloxicam® 7.5mg tab	284	0.03	23.48 (±10.58)	6667.85	0.01	0.39
TOTAL	**954241**	**100.00**	**60.52 (±68.13)**	**57752267.02**	**100.00**	**1.00**

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