A Review of the Prescribing Patterns of Combination Analgesics in the Private Health Care Sector.

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Abstract

Title: A review of the prescribing patterns of combination analgesics in the private health care sector.

Keywords: combination analgesics, drug utilisation review, generic, innovator, managed health care, pain, pharmacoeconomics, pharmaco-epidemiology, private health care sector.

South African prescribers have a large choice of combination analgesic preparations available for prescribing. According to Desmeules *et al.* (2003:8) the advantages of combining analgesics include increasing the duration of analgesia, widening the spectrum of efficacy, improved patient compliance and reduced parenteral abuse potential. According to McMahon (1975:13) one of the principle arguments against fixed-dose combinations is that the physician surrenders flexibility in managing his patient. Combination analgesics may expose patients to ingredients not necessary for pain relief in their particular condition (Beaver, 1984).

Rigas (1997:454) explains that the value of pharmaco-economics in providing cost-effective pharmacologic treatment for pain must not only be seen as a containment effort, but rather as a valuation effort. Meaningful economic analyses based on empiric information about cost and a range of subjective and objective outcomes are needed to minimise cost without compromising care.

The objective of this study was *to review and interpret the prescribing patterns of combination analgesics and the cost associated with their usage for the period 2001-2006 in a section of the private healthcare sector in South Africa.* This research can be classified as a quantitative, retrospective drug utilisation review study. Data were obtained from a medicine claims database, and the study population consisted of all combination analgesic prescriptions (Mims® category 3.3) for the period 1 January 2001 to 31 December 2002 and 1 January 2004 to 31 December 2006.

Firstly pain and the treatment thereof with combination analgesics were investigated from the literature to understand the disease and to determine the prevalence and treatment thereof. Secondly, managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology were investigated from the literature to understand these concepts. The influence of the South African government on the medicine pricing regulations was discussed.

Thirdly, through the empirical investigation the utilisation patterns of combination analgesics were reviewed, analysed and interpreted. It was determined that combination analgesic drugs represented 8.87% (n=261 907) of all medicine claimed during 2001 (N=2 951 326), decreased to 7.20% (n=381 809) during 2004 (N=5 305 846) after which it increased to 7.92% (n=187 745) in 2006 (N=2 370 572). Between 2001 (N=R379 708 489.00) and 2006 (N=R279 160 832.00) the cost percentage of the combination analgesic drugs decreased from 4.95% (n=R18 798 202.42) to 3.15% (n=R8 791 228.57).

The average cost per combination analgesic drugs decreased from R71.77 ± 61.67 to R46.83 ± 43.41 between 2001 and 2006. This decrease was of no practical significance ($d<0.8$). The average number of combination analgesics per prescription stayed relatively constant varying between 1.01 ± 0.11 in 2001 and 1.02 ± 0.13 in 2006.

The percentage generic combination analgesic drugs claimed increased from 29.63% (n=77 608) in 2001 to 66.37% (n=124 600) in 2006 (N=261 907 for 2001 and N=187 745 for 2006) even though generic medicine items claimed by the total database only increased from 26.79% (n=790 548) in 2001 to 40.27% (n=954 561) during 2006 (N=2 951 326 for 2001 and N=2 370 572 for 2006).

The combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg (e.g. Myprodol® capsules, Mybulen® capsules, Gen-payne® capsules and Ibupain Forte® capsules) represented the active ingredient combination with the highest prevalence for the entire study period, increasing from 28.44% (n=74 483) in 2001 to 33.08% (n=62 100) in 2006 of all combination analgesics prescribed (N=261 907 for 2001 and N=187 745 for 2006).

Generic substitution influenced the prevalence of the innovator medicine item, Myprodol® Capsules dramatically, causing a decrease from 23.16% (n=60 631) in 2001 to 3.77% (n=7 084) in 2006

representation of all combination analgesic prescribed. In 2006, the generics of Myprodol® Capsules e.g. Dentopain Forte®, Mybulen® Capsules, Gen-payne® and Ibupain Forte® represented 23.79% (n=44651) of all combination analgesics claimed.

Recommendations were derived regarding certain aspects of the clinical and economical management of pain e.g. the implication of generic substitution with regard to cost and prescribing patterns, and the decreasing cost of combination analgesics which might encourage abuse, needs further investigation.

Opsomming

Titel: 'n Evaluering van die voorskryfpatrone van kombinasie analgetika in die private gesonheidsorgsektor.

Sleutelwoorde: Kombinasie analgetika, pyn, bestuurde gesondheidsorg, farmako-ekonomie, farmako-epidemiologie, medisyneverbruiksevaluering, oorspronklike (innoveerder), generies, private gesondheidsorgsektor.

Suid-afrikaanse voorskrywers het 'n groot verskeidenheid van kombinasie analgetiese preperate beskikbaar om voorteskryf. Volgens Desmeules *et al.* (2003:8) sluit die voordele van analgetiese kombinasies die volgende in: 'n verlengde werkingsduur; 'n breër spektrum van effektiwiteit; verhoogde pasiënt meewerkendheid en verlaagde parenterale-misbruikpotensiaal. Volgens McMohan (1975:13) is een van die hoof argumente teen vaste-dosis kombinasies dat die voorskrywer fleksiteit t.o.v die bestuur van die pasiënt verloor. Kombinasie analgetika kan "pasiënte bloodstel aan bestandele wat onnodig is vir pynverligting van hul spesifieke kondisie" (Beaver, 1984).

Rigas (1997:454) verduidelik dat die waarde van farmako-ekonomie vir die voorsiening van koste-effektiewe farmakologiese behandeling van pyn nie slegs as 'n insluitingspoging gesien moet word nie, maar eerder as waarderingspoging.

Die doel van hierdie studie was om die voorskryfpatrone en geassosieerde koste van kombinasie analgetika in 'n gedeelte van die private gesonheidsorgsektor van Suid-Afrika te evalueer vir die periode 2001 tot 2006. Hierdie navorsing kan geklassifiseer word as kwantitatiewe, retrospektiewe medisyneverbruiksevaluering studie. Data was verkry vanaf 'n medisyne-eis databasis, en die studiepopulasie het bestaan uit al die kombinasie analgetika voorskrifte (MIMS® kategorie 3.3) van die jare 1 Januarie 2001 tot 31 Desember 2002 en 1 Januarie 2004 to 31 Desember 2006.

Eerstens was pyn en die behandeling daarvan met kombinasie analgetika ondersoek sodat die siekte verstaan kan word en die voorkoms en behandeling daarvan bepaal kan word. Bestuurde

gesondheidsorg, medisyneverbruiks evaluering, farmako-ekonomie en farmako-epidemiologie is tweedens bestudeer, sodat hierdie konsepte verstaan kan word. Die invloed van die Suid-Afrikaanse regering op medisyne prysregulasies is ondersoek.

Derdens was die verbruikspatrone van kombinasie analgetika ondersoek, ontleed en geïnterpreteer. Kombinasie analgetiese middels het 8.87% (n=261 907) van alle medisyne ge-eis tydens 2001 (N=2 951 326) verteenwoordig. Die waarde het afgeneem na 7.20% (n=381 809) tydens 2004 (N=5 305 846) waarna dit toegeneem het na 7.92% 9n=187 745) tydens 2006 (N=2 370 572). Tussen 2001 (N=R379 708 489.00) en 2006 (N=R279 160 832.00) het die koste persentasie van kombinasie analgetiese middels afgeneem vanaf 4.95% (n=R18 798 202.42) na 3.15% (n=R8 791 228.57).

Die gemiddelde koste per kombinasie analgetiese middel het afgeneem vanaf R71.77±61.67 na R46.83±43.4 tussen 2001 en 2006. Die afname in gemiddelde koste was prakties nie-beduidend ($d<0.8$). Die gemiddelde aantal kombinasie analgetika items per voorskrif het realtief konstant gebly en was 1.01±0.11 vir 2001 en 1.02±0.13 vir 2006.

Die persentasie generiese kombinasie analgetika middels ge-eis het toegeneem vanaf 29.63% (n=77 608) in 2001 tot 66.37% (n=124 600) in 2006 (N=261 907 vir 2001 en N=187 745 vir 2006), alhoewel die generiese medisyne items ge-eis deur die totale databasis slegs toegeneem het vanaf 26.79% (n=790 548) in 2001 tot 40.27% (n=954 561) tydens 2006 (N=2 951 326 en N=2 370 572 vir 2006).

Die kombinasie van ibuprofeen 200mg, parasetamol 250mg an kodiënfosfaat 10mg (bv. Myprodol® kapsules, Mybulen® kapsules, Gen-payne® kapsules en Ibupain Forte® kapsules) verteenwoordig die aktiewe bestandeel kombinasie met die hoogste voorkoms oor die volle studietydperk. Die kombinasie se voorkoms persentasie het toegeneem vanaf 28.44% (n=74 483) in 2001 na 33.08% (n=62 100) in 2006 van alle kombinasie analgetika ge-eis (N=261 907 vir 2001 en N=187 745 vir 2006).

Generiese vervanging het die voorkoms persentasie van innoveerder medisyne items bv. Myprodol® kapsules drasties beïnvloed. Myprodol® kapsules se voorkoms persentasie van alle kombinasie analgetika ge-eis het afgeneem vanaf 23.16% (n=60 631) in 2001 tot

3.77% (n=7 084) in 2006. Myprodol® kapsules se generiese bv. Dentopain Forte®, Mybulen® kapsules, Gen-payne® en Ibupain Forte® het in 2006 23.79% (n=44 651) van alle ge-eisde kombinasie analgetika verteenwoordig.

Aanbevelings is gemaak aangaande sekere aspekte van die kliniese en ekonomiese beheer van pyn bv. die implikasie van generiese vervanging t.o.v koste en voorskryfpatrone, en die verminderende koste van kombinasie analgetika wat kan aanleiding gee tot misbruik.

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Chapter 1
Introduction

1.1 Introduction

In accordance with a medicine claims database, it was the aim of this dissertation to shed some light on the prescribing- and usage patterns of combination analgesics. This was done with specific reference to the economic aspect of combination analgesic drug utilisation in South-Africa.

1.2 Problem statement

> A major challenge for the future lies in providing clinically effective and cost-effective pharmacotherapy and other services for the comprehensive management of pain (Rigas, 1997:454).

Furthermore promoting and providing quality, therapeutic, and cost-effective prescribing takes a joint effort from both physicians as well as pharmacists (Rigas, 1994:454). Cost-effectiveness and cost-utility analyses should allow the value of health care products and services to be defined to ensure the wise spending of health care funds.

Due to the escalating cost of medical care, manufacturers and consumers of medical instruments and pharmaceutical products now recognise the need to evaluate and compare the cost of investments and expenditures regarding the therapeutic effects achieved (Oreskovic, 2002:27).

According to Liedgens *et al.* (2005:790) an example of cost-effective pharmacotherapy for the comprehensive management of pain is tramadol/paracetamol combination analgesics. It is cost effective compared to non-steroid anti-inflammatory drugs (NSAID's) combined with proton pump inhibitors for the treatment of osteoarthritis related pain over a period of 6 months regardless of the risk of gastro-intestinal (GI) or renal complications. Tramadol®/paracetamol is also cost effective compared to the treatment with only NSAID's and NSAID's plus Histamine H2-antagonists (H2RAs) for patients at medium and high risk of gastro-

intestinal adverse events and in all cases if considering renal adverse events. Despite not being quantified in monetary terms, the lower incidence of adverse events with tramadol/paracetamol constitutes as a clinical benefit.

Beaver (1984:38) states that six rationales for using combination analgesics are identified. Most combinations however are formulated with the following two rationales in mind:

a) Enhancement of analgesia (Beaver, 1984:38); and

b) Reduction of adverse effects by combining two analgesics with different mechanisms of action (Beaver, 1984:38).

South African doctors have a large choice of combination analgesic preparations available for prescribing. These preparations contain various combinations of analgesics such as paracetamol, codeine, propoxyphene, and meprobamate. They may also be supplemented with non-steroidal anti-inflammatory agents (NSAID's), and many other additives like caffeine, antihistamines, amino acids, and vitamins (Raff, 2002:35).

Truter (1998:92) stated that out of four metropolitan areas in South-Africa, one-third (33.1%) of all prescriptions for central nervous system (CNS) drugs were for combination analgesics. Prescription data from fifty medical practices in each area were obtained from a medical aid scheme, and were retrospectively analysed for 1995. After the study was completed it was recommended that further studies on combination analgesic prescribing patterns should be undertaken, especially in relation to the diagnoses for which they were prescribed, as well as to other medications taken concurrently with analgesic products.

According to Myers *et al.* (2003:367) over-the-counter (OTC) and prescription medicine misuse places a burden on health and social services in South-Africa. Analgesic misuse is most often accounted for by the use of codeine-containing medicines, many of which are available over the counter. The average medication intake per migraine patient per day is 3 to 4 tablets and in 75,2% of the cases these patients abuse simple analgesics - isolated or in combination with other substances (Krymchantowski, 2003:44).

Taljaard (2002:132) suggested that research should be done on the combination analgesic medicine items which have the highest cost percentage in their corresponding groups, as it can serve as an indicator for cost sufficiency on expensive analgesic protocols.

Rigas (1994:454) explains that the value of pharmacoeconomics in providing cost-effective pharmacologic treatment for pain must not

only be seen as a containment effort, but rather as a valuation effort. Meaningful economic analyses based on empiric information about cost and a range of subjective and objective outcomes are needed to minimise cost without compromising care.

From the discussion above, it is imperative that research should be done regarding the necessity of combination analgesics as well as the utilisation and cost implication associated with these drugs.

1.3 Research question

The following research questions can be formulated on the basis of the preceding discussion:

- How can pain be conceptualised and what are the treatment characteristics of pain management?
- How can combination analgesics be conceptualised?
- How is pharmacoeconomics, pharmaco-epidemiology and drug utilisation review applied in the private health sector?
- What does the term managed health care entail?
- What is the prevalence of combination analgesic treatments and its associated costs within the private health care sector of South Africa?
- How does the prescribing, prevalence and usage of generic combination analgesics differ from the innovator drugs in the South African private health care sector?
- Is combination analgesics sometimes prescribed together with other analgesics?
- What recommendations can be made regarding the prescribing patterns and costs of combination analgesics in South Africa?

1.4 Research objectives

1.4.1 General objective

The general objective of this study was to review and interpret the prescribing patterns of combination analgesics and the cost associated with their usage for the period 2001-2006 in a section of the private healthcare sector in South Africa. A medicine claims database was used as primary source to obtain the necessary data.

1.4.2 Specific objectives

The specific objectives of the literature survey were as follows:

- To conceptualise pain and the treatment protocols thereof from available literature;
- To review combination analgesics and conceptualise the usage from the literature;
- To review the South African health care system; with special reference to the private health care system;
- To conceptualise managed health care, drug utilisation review , pharmacoeconomics and pharmaco-epidemiology from the literature; with special reference to the usage of combination analgesics.

The specific objectives of the empirical study were as follows:

- To investigate the prevalence and cost relationship of combination analgesics in relation to all the medicine items on the database;
- To investigate the prevalence and cost relationship of combination analgesics in relation to analgesic medicine items on the database;
- To compare the cost impact of the usage of generic combination analgesics and innovator products;
- To compare the cost-analysis of the different active ingredient combinations;
- To analyse the usage and prescription patterns of different combination analgesics, according to trade names, as well as the costs associated with these drugs according to the database;
- To analyse the average number of combination analgesic prescriptions per patient per year;
- To identify combination therapy of analgesics and determine the costs associated with these combinations;
- To analyse the prevalence of combination analgesics available without prescription;
- To possibly lift out other aspects which may require further investigation.

1.5 Research method

In order to accomplish the set objectives, the research method comprised of two phases, namely a literature and an empirical investigation.

1.5.1 Phase 1: Literature survey

The literature survey was divided into two steps.

Firstly the stipulation of extensive information on analgesics, specifically concentrating on combination analgesics and the usage thereof.

Secondly focussing on pharmacoeconomics, pharmaco-epidemiology, drug utilisation review and disease management, all of which are utilised to ensure optimal healthcare.

1.5.2 Phase 2: Empirical study

The empirical study was divided into several steps, namely:

- *Selection of a research design*

A non-experimental, quantitative, retrospective design was utilised in order to obtain the essential outcomes and achieve the specific objectives for this study.

- *Composition of population*

The study population was selected from a medicine claims database, which includes all the combination analgesics treatments that were recognised on the database. The intended population was over a five-year period stretching from 1 January 2001 to 31 December 2002 and from 1 January 2004 to 31 December 2006. The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for the whole 2003, therefore the usage and costs of drugs associated with this period cannot be compared with the other periods.

The following fields were used in the study:

The Nappi code, description (trade name), quantity dispensed, patient number, price, prescription number, date of dispensing and indicator for generic or innovator product of each drug.

No clinical data or demographic information, such as age, gender and race was available on the database, therefore the relevance of some of the utilisation patterns could not be determined.

Data for the analysis were obtained from one medicine claims database, thus, limiting external validity, implying that results can only be generalised to the specific database used, as well as to the specific study population.

- *Selection and application of criteria and measuring instruments for data analysis*

Measuring instruments and statistical calculations applicable to this study were implemented. The measuring instruments and statistical calculations used during this study were discussed in section 4.7.3 and 4.7.4.

- *Data application and data analysis*

The application of the data was achieved by viewing the criteria retrospectively; there after the data analysis was conducted by means of the Statistical Analysis System®, SAS 9.1® (SAS Institute Inc.).

- *Reliability and validity of research instruments*

The data utilised in this study were obtained directly from the central medicine claims database, thus no direct manipulation of the data was possible. The research will be conducted with assumption that all data obtained from the database were valid and correct.

During this study, all patient information was kept confidential. The database contained no patient names or personal details. The data used in this study was analysed with permission of *Interpharm Data systems (Pty.) Ltd.*, the database from which the data was derived.

- *Report and discussions of empirical investigation*

The report and discussion of the results of the empirical investigation was illustrated graphically or in tables to achieve the set claims of the empirical investigation. A detailed overview of the reports and discussion will follow in chapter 5 of the dissertation.

- *Conclusion and recommendations based on the results of the empirical study as well as the limitations of the study*

A conclusion based on the results of the literature survey and the empirical investigation, as well as the recommendations derived from this study on the prescribing patterns of combination analgesics will be offered in chapter six. The limitations encountered during the study throughout chapters four and five with a further detailed discussion of these limitations will be brought to attention in chapter six.

1.6 Division of chapters

The division of chapters will be as follows:

Chapter 1: Introduction.

Chapter 2: Analgesics and the usage of combination analgesics.

Chapter 3: Healthcare – concepts and approaches.

Chapter 4: Empirical investigation.

Chapter 5: Results and discussion.

Chapter 6: Conclusions and recommendations.

1.7 Chapter summary

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

Chapter 2
Analgesics and the usage of combination analgesics

2.1 Introduction

This chapter aims to discuss analgesics and the usage of combination analgesics as well as aspects of pain and its management.

2.2 Pain

2.2.1 A definition of pain

Pain is defined as

> an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (The International Association for the Study of Pain, 2006).

The International Association for the Study of Pain (IASP) (2006) also notes that pain is always subjective and that individuals describe their experience as pain, and if they report it in the same way as pain caused by tissue damage, it should be accepted as pain.

According to Katz (1998:2), the actual or potential nerve damage is mediated by specific nerve fibres to the brain where its conscious appreciation may be modified by various factors. However, as described by Serpell *et al. (*1998:31), the perception of pain is not simply a biological response, but rather a complex interaction that involves sensory, emotional and behavioural factors.

The more commonly known signs and symptoms related to health problems are pain and movement dysfunction. These key problems predominate, regardless of whether the problem is one of injury or illness (e.g. osteoarthritis, stroke, or cancer); regardless of which bodily system is primarily affected (e.g. neurological, musculoskeletal, cardiovascular or visceral); and regardless of the age or gender of the affected individual (Simmonds, 2006:175).

2.2.2 Classification of pain

According to Banks and Watkins, as quoted by Neugebauer (2007:1) it is difficult to classify pain, because there is an important but not well-understood issue in pain research – namely the different mechanisms of acute and chronic types of pain. Increasing evidence suggests that chronic pain is not simply the prolonged presence of acute pain.

On the other hand, pain classifications have been based on duration, etiology or pathophysiology, intensity and symptoms. However, according to Higson (2005), different classifications can merge and many people suffer from combinations of acute and chronic pains, neuropathic and nociceptive pain. The skill and ability of the practitioner and/or pharmacist will determine the most appropriate outcome for each patient.

2.2.2.1 Classification by Etiology

Chronic pain has been classified by pathology as nociceptive (due to ongoing tissue injury) or neuropathic (resulting from damage to the brain, spinal cord, or peripheral nerves), with mixed or undetermined etiologies. Analgesics are generally effective for nociceptive pain, but less effective for neuropathic pain (Feinberg 2000:45).

- *Neuropathic pain*

Holdcroft and Power (2003:635) states that neuropathic pain is a clinically important example of a diagnostic tag, failing to predict therapeutic outcome. The pain is initiated or caused by a primary lesion or dysfunction in the nervous system, and yet its cause is heterogeneous and may be inflammatory, metabolic or ischemic. Therefore a new classification has been proposed. The main approach is to divide peripheral neuropathic pain into stimulus evoked pain or stimulus independent pain (spontaneous pain). Spontaneous pain mainly arises by spontaneous activity in primary sensory neurones, and drugs that diminish neuronal activity in ion channels are prime targets for research. In contrast, stimulus evoked pain can be precisely measured by quantitative sensory testing.

In neuropathic pain, damage to or dysfunction of neurons causes pain and may also result in abnormal pain transmission. Neuropathic pain is pain produced by damage to or dysfunction of neurons in the peripheral or central nervous system (Hassinger & Hayes, 2006:3).

Table 2.1: Characters of neuropathic pain. Adapted from Serpell *et al.*, (1998:32).

	Central	Mixed	Peripheral
Site	Central pain (thalamic infarct)	Plexus avulsion, post herpetic neuralgia.	Neuroma, nerve compression, phantom, neuralgias, painful polyneuropathy, reflex sympathetic dystrophy, causalgia.
Character	Burning, pressing, squeezing, itching, tingling, numbness, and constant +/- intermittent shooting as well as an electric sensation.		
Common causes	Tumors that lie close to neural structures, cancer actually infiltrating the nerves or spinal cord and damage to the nervous system caused by cancer treatment (chemotherapy, radiation or surgery).		

- *Nociceptive pain*

Nociceptive pain involves activation of nociceptors – sensory nerve endings found in tissues – by noxious stimuli, and transmission of pain signals via afferent neurones to the dorsal horn of the spinal cord. Nociceptive pain acts as an early warning system by announcing the presence of stimuli that could damage normal tissue (Hassinger & Hayes, 2006:3). According to Wells *et al* (2003:357) nociceptive (acute) pain is somatic (arising from skin, bone, joint, muscle or connective tissue) or visceral (arising from internal organs such as the large intestine or pancreas).

Table 2.2: Characters of nociceptive pain. Adapted from Serpell *et al.* 1998:32.

	Somatic	Visceral
Site	Cutaneous (body surface), deep tissues (musculoskeletal tissues).	Sympathetically innervated organs can be transferred to body surface.
Character	Constant, localised, aching, throbbing, gnawing.	Vague distribution and quality. Deep, aching, dragging, squeezing. Acute: colic, sweating, blood pressure and heart rate fluctuations.
Common causes	Metastasis of the bone and post-surgical pain from surgical incision.	Pancreatic cancer and metastases in the abdomen.

2.2.2.2 Classification according to duration

- *Acute pain*

Acute pain has been described by Beers and Berkow (2006) as:

> an essential biologic signal of the potential for, or the extent of injury.

As:

> pain that lasts or is anticipated to last a short time.

Acute pain is defined by Hassinger and Hayes (2006:2) as:

> the normal, predictable, appropriate response to a noxious stimulus or disease process that threatens or produces tissue injury, and that abates following remission of the stimulus or healing of the injury.

Thus, as Grichnik and Ferrante (1991:217-220) describes it:

> acute pain is provoked by a specific disease or injury and is associated with muscle spasm and sympathic nervous system activation.

According to Beers and Berkow (2006) acute pain is often associated with anxiety and with hyperactivity of the sympathic

nervous system (e.g. tachycardia, increased respiratory rate, escalating blood pressure, diaphoresis and dilated pupils).

- *Chronic Pain*

Chronic pain is defined by Hassinger and Hayes (2006:2) as:

> pain associated with a chronic disorder, or pain that persists beyond resolution of an underlying disorder or healing of an injury, and that is often more intense than the underlying process would predict.

According to Beers and Berkow (2006) chronic pain has no adaptive biologic role and that vegetative signs (e.g. lassitude, sleep disturbance, decreased appetite, loss of taste of food, weight loss, diminished libido, constipation) often develop gradually, and depression may follow.

Serpell *et al.* (1998:44) stipulates that there is a significant proportion of patients that do not recover fully from acute pain, although most patients do. With more complete and prolonged analgesic agents, it is possible to make an impact on the number of patients who develop chronic pain.

Table 2.3 The difference between acute and chronic pain (Baumann, 2006).

Acute pain	• Chronic pain
• Short duration/abrupt onset • Universal • Understandable in terms of a response to a harmful stimulus • Single cause • Biomedical model appropriate • Accurate diagnosis and prognosis • More easily treatable	• Persists beyond the time expected for resolution/gradual onset • Non-universal • Less understandable in terms of a response to a stimulus • Multifactorial • Biomedical model inadequate • Diagnosis and prognosis uncertain • Less easily treatable

2.2.3 Mechanism of pain

According to Serpell *et al.* (1998:44):

> pain is a dynamic process, that sets in motion certain facilitory and inhibitory mechanisms, which respectively enhance or diminish the pain depending on the balance of the two opposing mechanisms.

These mechanisms are varied and multiple, which reaffirms the belief that enhancement in anti-nociception, must involve modulation of several target sites.

These changes occur on three main levels namely, peripheral, spinal and supraspinal. This implies that, in addition to combining analgesics with different sites of action, we should be directing them at two or more levels simultaneously. The balance between these mechanisms determines whether the nervous system goes on to develop dysfunction on a permanent basis and produce a chronic pain state (Serpell *et al.*, 1998:44).

According to Rang *et al.* (2003:562) it is necessary to distinguish between two components which may be implicated in pathological pain states. Firstly, the peripheral nociceptive afferent neuron, which is activated by noxious stimuli and secondly the central mechanisms by which the afferent input generates a pain sensation (Rang *et al.* 2003:562).

According to Wells *et al.* (2003:357) the stimulation of free nerve endings known as nociceptors is the first step leading to the sensation of pain. These receptors are present in both somatic and visceral structures and activated by mechanical, thermal, and chemical impulses. Release of Bradykinins, K^+, prostaglandin's, histamine, leikotrines, serotonin, and substance P can sensitise and/or activate nociceptors. Receptor activation leads to action potentials that are transmitted along afferent nerve fibres to the spinal cord. Action potentials persist from the site of noxious stimuli to the dorsal horn of the spinal cord and then rise to higher centres. The thalamus acts as a relay station and passes the impulses to central structures where pain is processed further (Wells *et al.*, 2003:357).

2.2.3.1 Mechanisms that maintain and amplify pain

According to Hassinger and Hayes (2006:4) chronic pain syndromes are driven in part by neurological mechanisms. For example, in some chronic pain syndromes, facilitatory influences on pain transmission from higher centres may be increased, and descending inhibitory influences may be increased, thus increasing pain transmission and perception (Hassinger & Hayes, 2006:4).

Hassinger and Hayes (2006:4) further explains that pain transmission itself may create functional and structural alterations in neurons that cause extra amplification and maintenance of the pain, which is also the phenomenon which is responsible for peripheral

and central sensitisation, two important mechanisms that maintain and amplify pain.

In sensitisation, peripheral or central pain, transmitting neurons develop a sharp excitability. This increase in neuronal sensitivity is due to a lowered threshold of activation and an increased responsiveness that may be caused in part by the reactive inflammatory process. The end result of sensitisation is that the patient feels disproportionately more pain (Hassinger & Hayes, 2006:4).

- *Peripheral sensitisation*

In peripheral sensitisation, there is an increase in excitability of peripheral nociceptors that amplifies pain signals to the central nervous system. Inflammatory mediators (PEG2, bradykinin, cytokines, and neuropathies) produced in inflamed tissue bind to receptors on nociceptors, altering their function on sensitising them. This causes increased pain signalling to the spinal cord and results in increased pain sensation (Hassinger & Hayes, 2006:4).

Peripheral sensitisation is thought to be an important mechanism underlying various features of nociceptive pain – such as spontaneous pain, hyperalgesia and allodynia (Schaible & Vanegas, 2000:800).

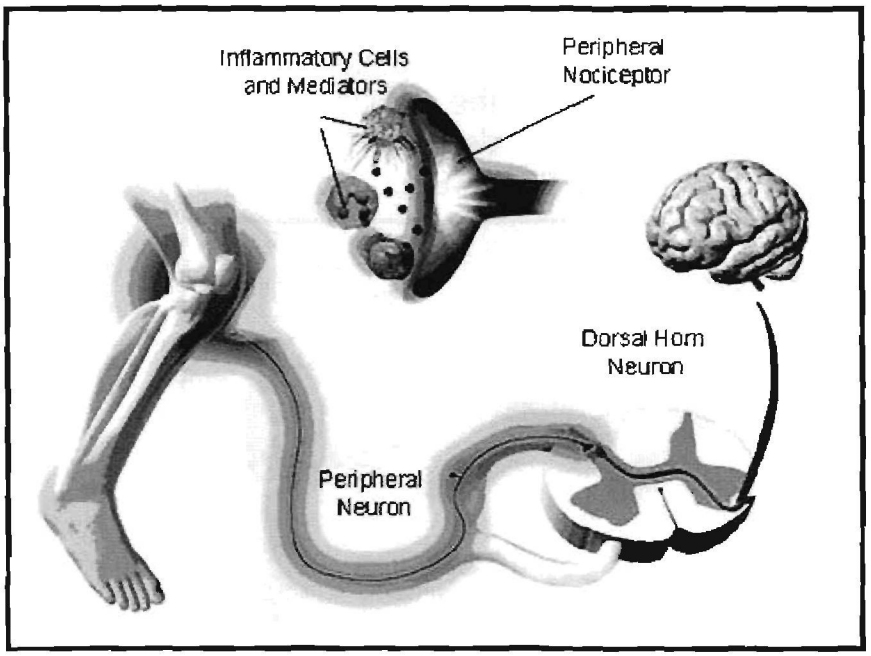

Figure 2.1 Peripheral sensitisation is an increase in the excitability of peripheral nociceptors that may be produced by an inflammatory process (Hassinger & Hayes, 2006).

- *Central sensitisation*

In central sensitisation, neurons that originate in the dorsal horn of the spinal cord become hyper excitable, increasing pain signals to the brain and thereby increasing pain sensation (Hassinger & Hayes, 2006:4).

According to Yunus (2007:481) the pathophysiological mechanisms of central sensitisation involve the activation of peripheral nociceptive C fibers in chronic pain by several chemicals (e.g. substance P, serotonin and bradykinin), following a painful stimulus (e.g. pressure or an inflammatory state). The C fibers carry the nociceptive impulses to the dorsal horn of the spinal cord which contains both nociceptive and non-nociceptive neurons. With intense impulses, both the nociceptive and the surrounding non-nociceptive neurons are activated, so that even a normally non-painful stimulus (e.g. touch) is now perceived to be painful – a phenomenon known as allodynia (Yunus, 2007:482).

Inflammatory mediators bind to receptors on pain-transmitting neurons in the dorsal horn of the spinal cord, altering their function and causing increased pain signalling to higher centres and increased pain sensation. Central sensitisation is an increase in the excitability of central pain-transmitting neurons that may be mediated by an inflammatory process (Hassinger & Hayes, 2006:4).

Central sensitasation is clinically characterised by hyperalgesia (excessive pain from a normally painful stimulus), allodynia, increase of pain from the site of the stimulus, and a post-stimulus lasting pain that is unpleasant, described as burning, throbbing, stinging or numbness (Yunus, 2007:482).

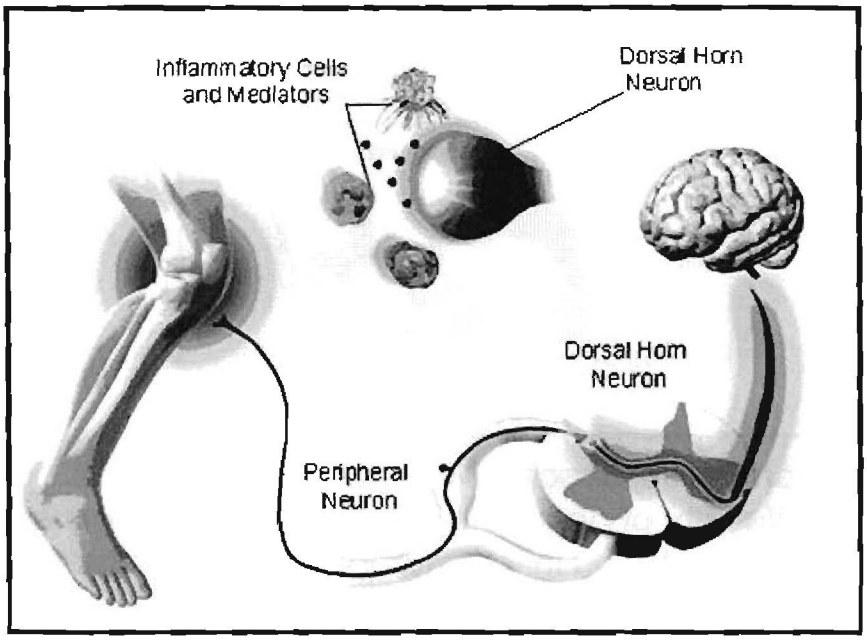

Figure 2.2 Central sensitisation is an increase in the excitability of central pain-transmitting neurons that may be produced by an inflammatory process (Hassinger & Hayes, 2006).

2.2.4 The social, economic and psychological implications of pain

According to Baumann (2005) pain is an integral part of the human condition which is

> a phenomenon that occupies the attention of a wide range of domains, including philosophy and religion, the arts and medical sciences.

According to Ables *et al.* (2006:341):

> pain is among the most common complaints in health care.

It accounts for considerable suffering and discomfort for patients, increased health care costs, a loss of productivity and is often associated with low self rated health (Ables *et al.*, 2006:341).

Zagari *et al.* (1996:356) states that persistent chronic pain often leads to complex social and psychological maladaptations, as well as substantial direct and indirect costs. Therefore, the proper

treatment of chronic pain involves pharmacological, behavioural and psychological interventions.

According to Ables *et al.* (2006:341) the psychosocial and psychiatric problems associated with pain makes its management complicated. Also, according to Zagari *et al.* (1996:356) the subjectivity of pain means that the assessment of the epidemiology, pharmacotherapy and economic costs of chronic pain is very difficult.

2.2.4.1 The bio-psychosocial factors that interact and modulate the experience of pain

According to Main and Williams (2002:534) psychological and social factors have been shown to play a major role in exacerbating the biological aspects of pain by influencing pain perception and the development of chronic disability.

According to Katz (2002:S2) exposure to low social support, low social anchorage or low social participation significantly increases the chance for experiencing a high level of pain. Holdcroft and Power (2003:635) also states that pain is not just caused by physical disorders, but the combinations of physiological, pathological, emotional, psychological, cognitive, environmental, as well as social factors which in turn play a vital role in recognising pain and pain levels.

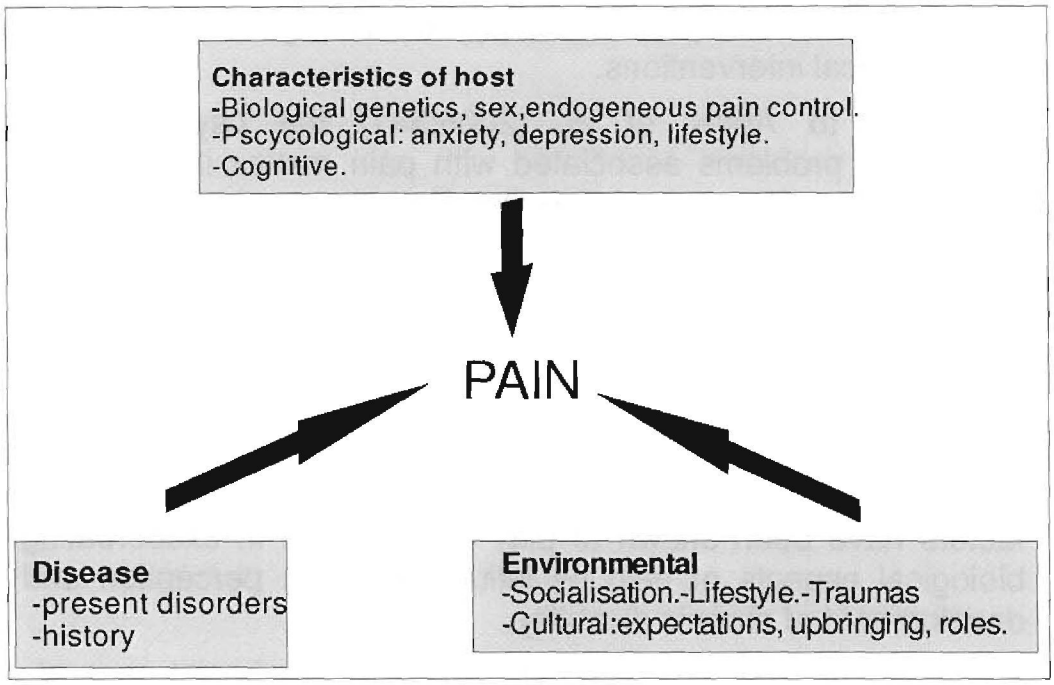

Figure 2.3 Bio-psychosocial factors that interact and modulate the experience of pain (Holdcroft & Power, 2003:635).

Raffa (2006:9) states that persistent pain represents a major burden and impact on life quality for patients and presents a major challenge for their physicians.

According to Miguel (2005:224) the assessment and management of pain is very difficult. Miguel (2005:224) also addresses the fact that pain is more than a singular sensation; it is influenced by emotional, cognitive, and psychosocial factors. Depression, anxiety, insomnia, and high neuroticism often coexist in chronic pain patients. This in turn complicates overall pain management and subsequently worsens the prognosis (Miguel, 2005:224).

According to Ables *et al.* (2006:341) cognitive-behavioural approaches to pain management have shown to be affective in lessening pain and functional disability.

Depression and chronic pain have a complex relationship, and depression is more common in chronic pain patients than in healthy patients. Pain, and possibly unconsciously, depression, may be treated with painkillers as a type of self-care (Turunen *et al.*, 2005: 378).

According to McWilliams and Asmundson (2007:31) many studies have supported the notion that pain-related anxiety and fear lead to chronic pain and increased disability.

2.2.4.2 Motivational implications of pain

Karoly and Reuhlman (1996:393) describe pain as:

> a powerful distress engendering or negative life event with the potential for triggering unpleasant self-appraisals as a result of its goal-interruptive qualities.

Distress has also been viewed by Karoly and Reuhlman (1996:393) in terms of self-defeating person-environment relations, often defined as involving:

- reductions in activity level;
- dependence on analgesic medication and medical intervention; and
- multiple dimensions of psychosocial impairment, usually focussing on depression and anxiety.

According to Karoly and Reuhlman (1996:393) research has shown that in patients referred to pain clinics, approximately one third meet standard diagnostic criteria for depression or anxiety.

In a study done by Karoly and Reuhlman (1996:393) it was found that the normative pain experience (i.e. pain in a non-clinical sample of adults) is associated with a distinctly negative pattern of work goal understanding in comparison to the work goal cognitions of individuals without pain. Goal cognition patterns account for variation in psychological status – depression and anxiety – over and above that caused by pain (Karoly & Reuhlman, 1996:393).

Katz (2002:S3) reported that pain is the third leading reason for absence from work in the United States, where the problem of chronic pain translates into an annual expenditure of at least $50 billion.

2.2.4.3 Economic implications of pain

According to Turunen *et al.* (2004:498) pain is a very common problem in a community. It is a major reason to visit a physician, thus the treatment of pain has a great economic impact on the health care system.

According to Loeser (1999:975) economic issues in pain management affect the patient, the provider and the society. Rigas (1996:456) states that a major challenge for the future lies

> in providing clinically effective and cost-effective pharmacotherapy and other services for the comprehensive management of pain (Loeser, 1999:975).

According to Rigas (1996:455) the worth of pharmacoeconomics in providing cost-effective pharmacologic treatment for pain should not only be seen as a containment effort, but rather as an assessment effort. Significant economic analyses based on empiric information about cost and a range of subjective and objective outcomes are needed to minimize cost without compromising care.

Rigas (1996:455) also emphasises that the costs of unalleviated pain can be very high if pain related complications need to be managed through additional drugs or if hospitalisation is needed for pain control.

2.2.5 Pain assessment/evaluation

Beers and Berkow (2006) states that when pain is being evaluated:

> the organic cause should always be sought out first, even if a prominent psychological contribution to the pain is likely, because pain is often managed best by removing the underlying cause.

According to Higson (2005) a poor outcome and increased burden for both patient and practitioner can be avoided if we listen to the patient, locate the pain and look at, and test the site of pain. An appropriate combination of resources should be used to best manage pain for each individual patient.

According to the Department of Health (DoH) (2003:265) pain should be assessed by:

- duration;
- severity thereof, i.e. sleeplessness due to severe pain;
- site;
- character-stabbing, throbbing, crushing or cramp like pain;
- persistent or intermittent;
- relieving or aggravating factors;
- accompanying symptoms;
- distribution of pain and
- referred pain.

The patient's history of pain should include:

> severity, site, quality, duration, course, timing (including frequency of remissions and degree of variation), exacerbating and relieving factors, and co-morbidities associated with the

pain (with emphasis on psychological issues, depression, and anxiety) (Beers and Berkow, 2006).

Furthermore, the use, effectiveness, and side effects of drugs and other treatments should be determined. The patient's level of function should be assessed in detail, focussing on family relationships (including sexual), social network, and employment or avocations (Beers & Berkow, 2006).

Beers and Berkow (2006) also point out that the meaning of pain for the patient should also be determined because reporting pain is more socially acceptable than reporting anxiety or depression, and appropriate therapy often depends on sorting out these perceptions. Furthermore, he patient's perception of pain can represent more than the pathology inherent to the disease (Beers & Berkow, 2006).

A physical examination is essential, often helping to identify underlying causes and to further evaluate the degree of functional impairment. Appropriate laboratory tests and X-ray examinations (Beers & Berkow, 2006).

2.2.6 Treatment of pain

2.2.6.1 The importance of pain management

According to Rang *et al.* (2003:562) pain is a disabling accompaniment of many medical conditions, and pain control is one of the most important therapeutic priorities.

Inadequate pain management can decrease quality of life, be an indication of poor quality of care (especially among patients near the end of life or in long-term care settings), and may also contribute to suicide (Beers, 2005).

Pain produces a physiological stress response that presents with increased heart and breathing rates to facilitate the increasing demands of oxygen and other nutrients to the vital organs. Failure to relieve pain produces a prolonged stress state, which can result in harmful multisystem effects (Middleton, 2003:28).

Within primary care, pain is the reason for many consultations and can be associated with the progression of many different conditions managed by nurses, doctors and pharmacists (Higson, 2005).

According to the Department of Health (2003:265) the objectives of pain management are:

- to establish the cause of pain, and to manage it appropriately; and

- to ensure total pain relief with minimal side effects.

Tintinalli *et al.* (2006) however, state that the goals of pain management are:

- Efficacy.
- No significant interference with evaluation of the underlying disease process.
- Rapidity of onset.
- Ease of administration.

While treatment of an underlying disease or pathology often yields pain resolution, pain can also be a symptom or disease in and of itself and must be treated accordingly (Ruane, 2006:36).

2.2.6.2 Risk factors associated with uncontrolled pain

Mann (2003:1320) states that patients should be informed of the dangers associated with inadequately managed acute pain, such as serious cardiovascular complications. Uncontrolled pain can also be the cause of symptoms such as sleep disturbance, anorexia, muscle wasting, and depression (Mann, 2003:1320).

2.2.6.3 Challenges of pain management for the 21st century

According to Langford (2006:2) pain is the foremost cause of morbidity internationally, with published data showing its prevalence as high as 50% for chronic pain in the European population.

Despite the high prevalence of pain, the majority of evidence indicates that it is often poorly managed within the health care environment. Inappropriate and insufficient assessment, advice and management of pain add to the health burden, suffering and dysfunction for the individual and for society (Simmonds, 2006:175).

According to Seers *et al.* (2006:5) it is clear that the challenge of optimal pain management is not being met for a variety of reasons, including a:

> lack of knowledge; the values and beliefs that affect judgements; how we make decisions and use evidence about pain management; and a lack of prioritisation of pain and its management both at an individual and institutional level.

According to Simmonds (2006:175) insufficient practitioner knowledge about pain management is often documented. Pain education for health professionals at all levels has been identified

repetitively as an important step towards changing ineffective pain management practices.

Seers *et al.* (2006:5) further states that:

> knowledge about pain on its own is not enough - good pain management is underpinned by competent decision-making.

Clinical decision-making is a multifaceted activity that takes place in a dynamic and often stressful environment.

The intricacy of pain management decision-making is compounded by the subjective character of pain, the crucial communication between patient and clinician to comprehend and treat the pain problem, and the dependent relationship promoted by the health care system (Seers *et al.*, 2006:5).

Although more informed patients insist on quality care, patients stay relatively inactive in managing pain problems. Even when the pain problem is understood and treatable, the result occurring after an action can still be determined by chance, despite a 'good' decision being made (Seers *et al.*, 2006:5).

Physicians face various challenges when prescribing analgesics to manage chronic pain in older patients:

- Analgesics are normally effective for pain due to ongoing tissue injury but less effective for pain resulting from damage to the brain, spinal cord or peripheral nerves (Feinberg, 2000:51).
- Drug regulations and patients attitudes about "addiction" may impede the prescription of opioid analgesics in cases where these agents would be useful (Feinberg, 2000:51).
- Older patients are at increased risk of medication side effects from most classes of drugs, including analgesics (Feinberg, 2000:51).

The challenge for pain management is about needs: we need to care about it; we need to know what to do, and do it competently; we need to collect evidence to show our progress. That way a partnership with the person in pain can be developed to meet the needs for pain management (Seers *et al.*, 2006:5).

2.2.6.4 Treatment of acute post-operative pain

According to Phero *et al.* (2004:210) in the treatment of acute pain:

> the ability to prevent the onset of pain in the immediate postoperative period, decrease its intensity, and interfere with the development of sensitisation contributing to hyperalgesia for days following a procedure can greatly benefit the patient,

> rather than post-operative attempts to decrease pain after it has reached full intensity (Phero et al 2004:210).

According to Phero *et al.* (2004:212) recent findings state that patients benefit from receiving optimal Non-steroid anti-inflammatory (NSAID) doses, because they are effective, relatively safe, and reduce the need for opioids. Once the dose of NSAID has been optimised, and if pain persists, then the use of opioids may be considered. A commercially available combination product containing an opioid and paracetamol may be a good option and is easy to prescribe. Paracetamol's site of action differs from that of NSAID's, and paracetamol's analgesic effect is considered synergistic when in combination with NSAID's and opioids (Phero *et al.*, 2004:212).

2.2.6.5 Non-pharmacological treatment

Pain is not only treatable with pharmacological approaches. According to Lichtman *et al.* (2006) non-pharmacologic treatments are widely used to manage pain and cope with emotional distress. These treatments include conventional techniques, like behavioural and cognitive behavioural therapies, as well as complimentary and alternative medicine interventions, such as food supplements and herbs, energy therapies and meditation, Furthermore, pain can also be managed at a peripheral level using ice packs, heat pads and massage (Lichtman *et al.*, 2006).

According to the Department of Health (DoH) (2003:265), non-drug treatment of pain includes patient counselling and lifestyle modification.

2.2.6.6 Pharmacologic therapy

According to Ruane (2006:37) the use of pharmaceutical products is the most common approach to managing pain, although they are often used in combination with other therapies. The intensity, underlying causes, frequency, duration, and type of pain determine the appropriate regimen (Ruane, 2006:37).

Tintinalli *et al.* (2006) identified the primary agents for the control of pain as the opioids, non-steroidal anti-inflammatory drugs (NSAID's) and paracetamol.

The World Health Organization's (WHO) three-step ladder for cancer control (fig. 2.4) has documented effectiveness in many settings (Tintinalli, 2006).

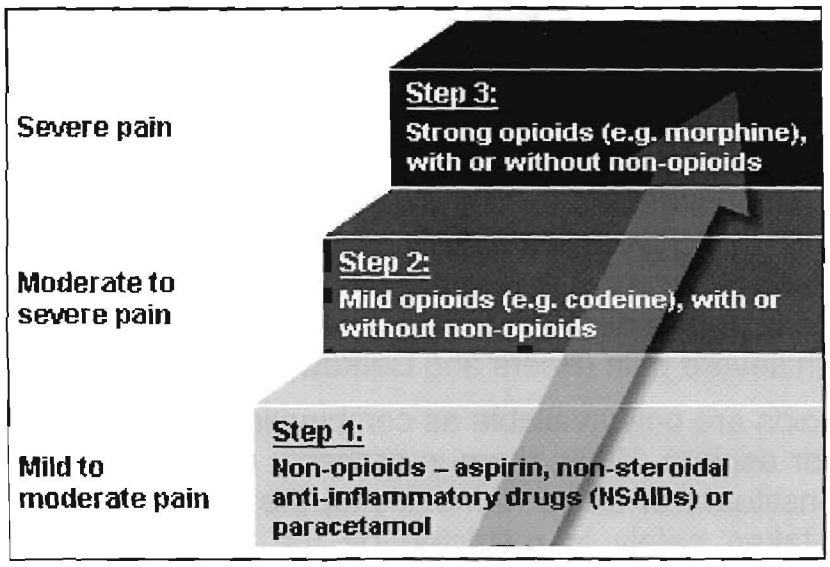

Figure 2.4 World Health Organization's three-step ladder for cancer pain control (WHO, 2007).

2.3 Analgesic drugs

2.3.1 Classification of analgesic drugs

The Monthly Index of Medical Specialities (MIMS) (Snyman, 2007:11a), classifies analgesics into four categories namely:

- Narcotic analgesics;
- Analgesics and antipyretics;
- Combinations and
- Other

2.3.1.1 Narcotic analgesics

According to Feinberg (2000:46):

> morphine-like opioids have been used for centuries to relieve pain.

According to Beers and Berkow (2006) opioid analgesics are extremely valuable in the treatment of severe acute pain, including post-operative pain, and chronic pain, including cancer-related pain. Opioid analgesics are often underused, resulting in needless pain and agony, because the required dosage is often underestimated, their duration of action and risk of side-effects are overrated, and physicians and nurses often have irrational concerns about the development of addiction (Beers and Berkow, 2006).

Feinberg (2000:46-47) states that a select group of chronic pain patients benefits from the careful use of opioids, resulting in pain reduction and improved physical and psychological functioning.

According to Beers and Berkow (2006) physical dependence occurs in virtually all patients treated for chronic pain with opioids for a long period, but still addiction is extremely rare in patients without a history of substance abuse. Therefore, physical dependence should not be considered in the decision to begin with or to increase doses in patients with severe pain (Beers and Berkow, 2006).

Most mild opioids are only available as combination analgesics (with paracetamol or aspirin). While there is probably no ceiling dose for the opioid constituent of these formulations, the number of tablets that can be taken safely is restricted by the amount of simple analgesic e.g. aspirin or paracetamol (Patt, 2006).

The most common opioid that is present in combination analgesics is codeine. According to Tintinalli (2006) codeine produces more nausea, vomiting, and dysphoria than other opioids.

According to Lichtman *et al.* (2006) current thinking distinguishes between two classes of opioid drugs namely *weak* and *strong*. Codeine, dihydrocodeine, tramadol, and dextropropoxyphene are good examples of the weak class, and are mostly marketed in combination with a non-opioid such as aspirin or as NSAID's. Morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl, and heroin are examples of the strong class.

2.3.1.2 Analgesics and antipyretics

Non-opioid analgesics fall into two categories: paracetamol and non-steroidal anti-inflammatory drugs (NSAID's). Included are salicylates such as aspirin, various classes of NSAID's, and the new cyclo-oxygenase-specific (COX-2) inhibitors (Feinberg 2000:45).

To make a choice between aspirin, paracetamol and NSAID's, e.g. ibuprofen, table 2.4 has proven to be of use.

Table 2.4 The difference between aspirin, paracetamol and ibuprofen.

Aspirin		
Indications - Mild to moderate pain - Inflammation - Pyrexia E.g. headache, toothache, mild rheumatic pain, sore throat and discomfort caused by a feverish illness. Rheumatoid arthritis if given regularly	**Contra-indications** - Children under 12 years - Haemophilia or bleeding disorders - Gastric or duodenal mucosal lesions or ulceration - Previous history of bronchospasm, asthma or allergy to aspirin or other NSAID's	***Cautions*** - Renal or hepatic impairment - Pregnancy or breast-feeding - Elderly-more prone to side-effects e.g. gastric irritation - Dyspepsia - Patients on warfarin
Paracetamol		
Indications - Mild to moderate pain. - E.g. headache toothache, joint pain. - Pyrexia	**Contra-indications** - Hypersensitivity to paracetamol	**Cautions** - Renal or hepatic impairment - Alcohol dependence - Liver damage following overdose
Ibuprofen		
Indications - Mild to moderate pain. - Inflammation - E.g. Muscle, bone and joint pain and stiffness, headaches, dysmenorrhoea - Pyrexia	**Contra-indications** - Previous or active peptic ulceration - Previous history of hypersensitivity precipitated by aspirin or other NSAID's	**Cautions** - Cardiac, renal or hepatic impairment - Pregnancy or breast-feeding - Elderly- more prone to side-effects e.g. gastric irritation - -Coagulation disorders - History of GI bleeding or ulceration - Asthma

2.3.1.3 Combination analgesics

Combination analgesics are discussed in 2.4.

2.3.1.4 Other

Analgesics classified as *other* by Snyman (2007:81) all include the active ingredient, tramadol (refer to section 2.4.8.16). According to Jung *et al.* (2004:1038) tramadol hydrochloride has weak opioid activity and produces analgesia through an opioid effect that binds mu-opioid receptors and modifies transmission of pain signals through inhibition of serotonin and norepinephrine reuptake within pain pathways of the central nervous system.

Clinical experience indicates that tramadol is associated with fewer adverse effects than typical opioids, notably respiratory depression, constipation, and potential for addiction (Jung *et al.*, 2004:1038).

2.3.2 Analgesic use during pregnancy

According to Hersh *et al.* (2000:527) over-the counter analgesics include numerous agents that should be avoided by pregnant women, especially late in their pregnancy.

In a study done by Rowland *et al.* (2005:660) maternal use of ibuprofen or codeine containing analgesics during the periconceptional period might be associated with an increased risk of certain cardiovascular malformations in infants.

Paracetamol, administered at therapeutic doses, is in general considered the best choice for treating minor pain and fever in pregnant patients (Black & Hill, 2003:2517).

According to Hersh *et al.* (2000:527) aspirin should be avoided, especially late in pregnancy, because it is related with delivery complications and postpartum hemorrhage. Therefore Black and Hill (2003:2517) also advise that pregnant women should use salicylates only under the guidance of a medical professional.

Aspirin and the newer NSAID's such as ibuprofen have the common mechanism of inhibiting prostaglandin synthesis. By blocking synthesis of uterotropic prostaglandins of the E and F series, drugs in the NSAID class have the capability to inhibit labour and prolong pregnancy therefore the use of aspirin or any other NSAID, especially during the third trimester of pregnancy, should be avoided (Hersh *et al.*, 2000:527).

The Medicines Control Council (MCC) (2006a:37), requires that all NSAID containing products should stipulate the following warning:

> Regular use of non-steroidal anti-inflammatory drugs during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

In addition to the above, the following special precaution should be included (MCC, 2006a:37):

> In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

2.3.3 Analgesic use in geriatrics

According to Aubrun and Marmion (2007:109) management of postoperative pain in elderly patients can be a very complicated task because older patients often have co-existing diseases and concurrent medications, diminished functional status and physiological reserve and age-related pharmacodynamic and pharmacokinetic changes.

According to Beers (2005) pain is more common amongst geriatrics than amongst younger adults and the prevalence may be higher among nursing home residents.

Therefore, analgesic drugs are more often used by older patients than non-drug therapies for the management of pain. Analgesics are not universally effective in all geriatric patients, but can be a great blessing for some older patients in chronic pain (Feinberg, 2000:44).

Pain assessment in elderly patients presents numerous problems caused by differences in reporting cognitive impairment and difficulties in measurement (Aubrun & Marmion, 2007:109).

According to Beers (2005) the elderly are more likely than younger people to experience adverse effects while using analgesics. Therefore, each older patient should be managed individually, and their medication intake should be determined by cost, benefit, potential adverse effects, and the patients other medical problems (Feinberg, 2000:44). Acetaminophen is the analgesic of choice for most elderly people with mild to moderate pain.

2.3.4 Analgesics and concomitant alcohol use

According to Hersh *et al.* (2000:528) the use of alcohol in combination with NSAID's (including aspirin) significantly increases the risk of faecal blood loss which is associated with gastro-intestinal erosions and ulcerations. Both alcohol and NSAID's are capable of damaging the gastric mucus, but alcohol may also stimulate gastric

acid secretion, thereby aggravating the gastro-intestinal toxicity of NSAID's (Hersh *et al.*, 2000:528).

In October 1998, the U.S. Food and Drug Administration (FDA) (1998:1) announced that all over-the-counter (OTC) pain relievers and fever reducers must carry a warning label advising people who consume three or more alcoholic drinks every day to consult their doctors before using these drugs because it may cause stomach bleeding or liver damage.

According to Hersh *et al.* (2000:528):

> hepatotoxicity is a complication of both prolonged alcohol use and paracetamol overdose.

The combination of alcohol and paracetamol induces a complicated drug interaction, depending on the specific scenario, and may lead to acute liver failure.

2.4 Combination analgesics

Combination analgesics combine two analgesics with different modes of action in a single tablet or capsule. Because they are in the same capsule, they are referred to as fixed-dose combinations, to distinguish them from a different way of combining analgesics, namely to give the drugs separately, in variable dose combinations (Anon, 2005).

2.4.1 The rationale behind combining analgesics

According to Curatolo and Sveticic (2002:507) the rationale behind combining drugs in pain management is based on two considerations. Firstly, single drugs do not always provide satisfactory pain relief. Therefore, combining drugs that act at different receptors and on different pain mechanisms may improve pain relief. Secondly, single drugs that provide acceptable pain relief may, at the same time, cause unacceptable side effects. Therefore, drug combinations may allow a decrease in the amount of the single components needed to achieve the same analgesic effect with a lower incidence of side effects (Curatolo and Sveticic, 2002:507).

According to Desmeules *et al.* (2003:8) other advantages of combining analgesics include increasing the duration of analgesia, widening the spectrum of efficacy, improved patient compliance and reduced parenteral abuse potential.

Raffa (2001:257) states that no singlular analgesic agent is perfect and no single analgesic can treat all types of pain. However each agent has distinct advantages and disadvantages compared to the

others. Therefore, clinical outcomes might be improved under certain circumstances with the use of a combination of analgesics, rather than dependence on a single agent (Raffa, 2001:257).

Schnitzer (2003:13) adds that:

> analgesic combinations provide the opportunity for better efficacy with less overall morbidity than provided by single analgesic agents.

According to Barkin (2001:433) and Altman (2004:110) enhanced pain relief can be demonstrated and adverse effects minimised by formulating analgesic combinations as the method to improve pain treatment. Barkin (2001:433) adds that:

> substantial evidence supports combining analgesics for the management of pain and, in some instance, they have a heterogeneous pharmacologic sparing effect. Fixed dose combination analgesics with demonstrated efficacy and safety are widely useful for pain management.

It should be emphasised that the World Health Organization (WHO) (2007) recommends that analgesia be administered according to a three step "Analgesic Ladder". This entails starting analgesic therapy with paracetamol. Should the paracetamol alone prove to be ineffective, then a NSAID should be added to the paracetamol. Should this also prove inadequate then an opioid should be added to the paracetamol/NSAID regime. Each of these substances acts on different receptors, thus their actions are synergistic.

According to Raff (2002:34), it would thus make pharmacological sense that a combination agent contain the three substances recommended by the WHO.

However, a number of arguments exist against the use of fixed-dosed analgesic combinations. These arguments as listed by Beaver (1984) include that:

> combinations limit flexibility and individualisation of dosage.

And that combination analgesics may:

> expose patients to ingredients not necessary for pain relief in their particular condition (Beaver, 1984).

Not all combinations or all dose rations of a combination lead to an enhanced analgesic effect or to reduced adverse events. Therefore, each combination and each dose ratio needs to be evaluated individually (Desmeules *et al.* 2003:11).

According to Desmeules *et al.* (2003:11) fixed-dose combinations are of worth only when they have been:

developed according to rational pharmacokinetic and pharmacodynamic criteria, and when claims for their benefits have been supported by evidence-based data and well-designed clinical studies.

2.4.2 Mechanism of action

According to Raffa (2006:10) rational combinations of analgesic drugs offer a viable approach to managing persistent pain that involves multiple sites/pathways.

The combination of two analgesic drugs has the potential to overcome tolerability, efficacy and time-to-onset limitations of the component drugs and, in certain cases, act synergistically to increase their analgesic effect. Combining analgesics with different mechanisms or sites of action, for example, can allow for reduced doses of the component drugs, reducing overall adverse effects with comparable analgesia (Raffa, 2001:260).

Figure 2.5 depicts typical sites of action for several analgesic classes.

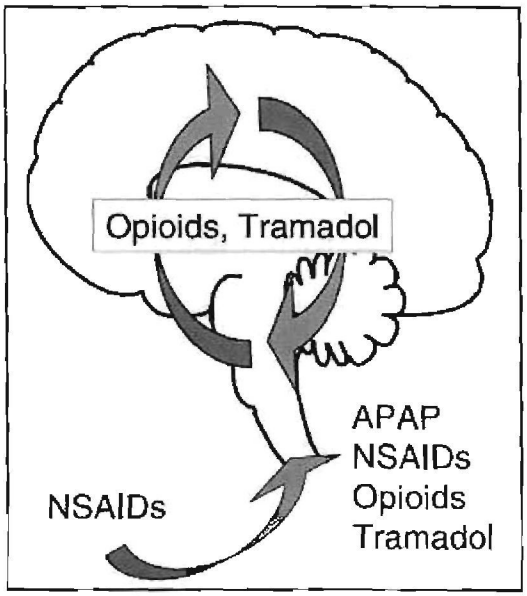

Figure 2.5 Major site(s) of action of analgesic classes (Raffa, 2001:258)

Likewise, combining short-acting and long-acting agents can result in both shorter onset and longer duration of analgesia (Raffa, 2001:260).

According to Raffa (2001:257) a combination analgesic is most effective when the individual agents act through different analgesic mechanisms and act synergistically. By activating multiple pain inhibitory pathways, combination analgesics can provide more

effective pain relief for a broader spectrum of pain, and might also reduce adverse drug reactions.

2.4.3 The potential benefits of combination analgesic prescribing

According to Raffa (2001:257) the use of combination analgesics vs. an individual agent offers several potential benefits:

- Combining analgesics into a single product may improve physician prescribing and patient compliance by reducing the total number of medications that a patient must take to manage pain (Raffa, 2001:257).
- Combining active ingredients with different mechanisms of action may also provide multimodal coverage of a broad spectrum of pain, and may enable the individual agents potentially to act in a greater than additive (synergistic) fashion (Raffa, 2001:257).
- Fixed-combination drugs are often less expensive for the patient than the individual ingredients baught seperately at the retail level (McMohan, 1975:10).
- In terms of safety, lower doses of each individual analgesic, may result in a lower incidence of individual adverse events (Raffa, 2001:257).

2.4.4 The potential disadvantages combination analgesic prescribing

According to McMahon (1975:13) one of the principle arguments against fixed-dose combinations is that the physician surrenders flexibility in managing his patient. In certain cases, the dosage of certain drugs should be individualised e.g. patients with liver or renal disease.

2.4.4.1 Undesirable drug interactions in combining analgesics

According to Desmeules *et al.* (2003:8) analgesic combinations can be considered to interact either pharmacokinetically and/or pharmacodynamically. A rationally developed analgesic combination should therefore fulfil certain pharmacokinetic and pharmacodynamic criteria.

Ideally, analgesic combinations should be screened for unwelcome pharmacokinetic and pharmacodynamic interactions in pre-clinical studies.

2.4.5 Pharmacokinetic interactions in analgesic combinations

In terms of pharmacokinetic criteria, unwanted interactions that affect the absorption, distribution, metabolism, or elimination of one or more of the drugs in combination should be avoided (Desmeules *et al.*, 2003:8).

According to Levy (1975:21) two or more drugs used in combination are likely to differ in terms of their biologic half-life and the factors that influence the half-life. A thorough assesment of risk-benefit aspects of fixed-dose drug combinations must take the following into consideration:

- the degree of inter-subject variation of the biologic half-life of each drug (Levy, 1975:21);
- the relationship between the half-life of each of the drugs in combination (Levy, 1975:21);
- the magnitude of inter-subject variation in the therapeutically effective concentration of each drug (Levy, 1975:21); and
- the therapeutic index of each drug (Levy, 1975:21).

The cytochrome P450 metabolic pathways are by far the most important pathways affected by the various pharmacokinetic drug interactions. An example of a drug affected by this kind of interaction is codeine, which is often used in analgesic combinations (Desmeules *et al.*, 2003:8).

Pharmacoeconomic criteria can be tested in clinical trials. Phase I studies should demonstrate bioequivalence between each drug in combination and when administered separately. These studies would additionally show whether the pharmacokinetics, including the half-lives of the respective drugs is compatible. If possible, data on the dose-concentration relation (from phase II trials), and the influence of co-variables such as age, gender, genetic factors, and renal and hepatic function on the pharmacokinetics of each component (from phase III trials) should be made available (Desmeules *et al.*, 2003:8).

2.4.6 Pharmacodynamic interactions in analgesic combinations

In terms of pharmacodynamic criteria, unwanted interactions may either increase the risks or intensity of side effects, to reduce effectiveness (Desmeules *et al.*, 2003:8).

According to Desmeules *et al.*, (2003:9) analgesic combinations should satisfy two important pharmacodynamic criteria, namely:

- Firstly, the components of the combination should display additive or synergistic analgesia. In other words, each component should contribute to the analgesic effect, and the analgesia achieved with the combination should be superior to that reached with any individual agent (Desmeules *et al.*, 2003:9).
- Secondly, the additive or synergistic interaction should allow lower doses of each substance to be used in combination, resulting in an improvement in the safety profile. For a given level of efficacy, the combination should display greater tolerability or a lower risk of side effects than each component drug (Desmeules *et al.*, 2003:9).

2.4.7 Drugs included in combination analgesics

2.4.7.1 Paracetamol

Paracetamol is an effective alternative to aspirin as an analgesic-antipyretic agent; however, its anti-inflammatory properties are much weaker (Burke *et al.*, 2006). According to Lifespan healthcare NHS (2006:3) paracetamol is normally favoured above aspirin especially in the elderly.

According to the American Food and Drug Administration (FDA) (2004:1) paracetamol has been marketed in the United States as an over-the-counter (OTC) antipyretic/analgesic agent since 1960. Paracetamol is available in a variety of strengths and formulations for adults and children as a single-ingredient product. It can also be found in various combination over-the-counter and prescription drug products.

Paracetamol is available without a prescription, and is widely used for its antipyretic qualities and analgesic properties (Osborne & Bryant, 2003:48).

- *Mechanism of action*

According to Lichtman *et al.* (2006) and Tintinalli (2006) it does not inhibit platelet function and is not anti-inflammatory, so it is useful in thrombocytopenic patients.

Paracetamol's mechanism of analgesic action has not been completely established; it is known to inhibit prostaglandin synthesis in the brain, but not peripherally, explaining the lack of anti-inflammatory characteristics (Gibbon, 2003:397).

According to Burke *et al.* (2006) paracetamol has a poor ability to inhibit cyclo-oxygenase (COX) in the presence of high peroxide concentrations, as are found at sites of inflammation.

Gibbon (2003:397) further notes that the antipyretic effect may be a result of the direct action centrally on the hypothalamic heat-regulating centre.

- *Pharmacokinetics and administration*

According to Burke *et al.* (2006) oral paracetamol has outstanding bio-availability because it reaches peak plasma concentrations within 30 to 60 minutes and the half-life in plasma is about 2 hours after therapeutic doses. Furthermore, paracetamol is relatively uniformly distributed throughout most body fluids.

> Some 90% to 100% of the paracetamol may be recovered in the urine within the first day at therapeutic dosing, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected (Burke *et al.*, 2006).

- *Clinical uses*

Paracetamol is useful in the treatment of pain and fever. It is usually well tolerated and is the drug of choice for relieving and treating mild to moderate musculoskeletal pain (Feinberg 2000:45).

- *Adverse effects*

According to Gibbon (2003:398) paracetamol has few adverse effects when used in therapeutic doses. In rare cases, hypersensitivity skin reactions, neutropenia and thrombocytopenia may present.

According to Mauck and Hurdle (2004:220) hepatotoxicity is a severe complication of paracetamol monotherapy. Gibbon (2003:398) explains that long-term administration of larger than recommended doses is the possible cause of nephro- or hepatotoxicity and that acute over dosage may lead to potentially fatal hepatic and renal necrosis. Age, malnutrition, and alcohol abuse are examples of independent risk factors for hepatotoxicity with paracetamol (Mauck & Hurdle, 2004:220).

2.4.7.2 Aspirin

- *Mechanism of action*

According to Gibbon (2003:397) the analgesic, the result of its ability to inhibit prostaglandin synthesis, both centrally and peripherally.

From a pharmacologic standpoint, aspirin can be viewed as an NSAID, but because of its commercial availability long before other NSAID's, it's often presented as a totally different entity from the newer NSAID's (Hersh *et al.*, 2000:505).

According to Gibbon (2003:397) aspirin's inhibitory effects on platelet aggregation and blood clotting may be due to its action in acetylating proteins and enzymes, and interfering with thromboxane synthesis.

- *Pharmacokinetics and administration*

According to Burke *et al.* (2006) orally ingested *salicylates* like aspirin are absorbed rapidly, partially from the stomach but mainly from the upper small intestine. Substantial aspirin concentrations are found in plasma in less than 30 minutes after a single dose was administered, and a peak value is reached in about 1 hour after which it declines gradually. The rate of absorption is determined by many factors, particularly the disintegration and dissolution rates of the tablets administered, the pH at the mucosal surface, and gastric emptying time (Burke *et al.*, 2006).

According to Gibbon (2003:397) aspirin should be administered orally and may reduce gastric irritation by ingesting it with food, because according to Burke *et al.* (2006) it delays absorption of salicylates. Rectal absorption of salicylate is generally slower than oral absorption and is incomplete and incoherent (Burke *et al.* 2006).

According to Levy (1981):

> salicylic acid is eliminated by renal excretion and by metabolic conversion to conjugates with glycine and glucuronic acid, respectively, and to gentisic acid.

Two of these metabolic processes are easily saturable, causing systemic clearance of salicylate to decrease with increased dosages.

According to Burke *et al.* (2006):

> *salicylates* are excreted in the urine as free *salicylic acid* (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl glucuronides (5%), and gentisic acid (less than 1%).

- *Clinical uses*

According to Gibbon (2003:397) aspirin can be used as an antipyretic in fever, for the pain and discomfort of dysmenorrhoea, for inflammatory disorders and for rheumatic fever. Anti-inflammatory effectiveness is only provided by high doses. Aspirin is

quite useful for treatment of conditions in patients who are not allergic to it (Lifespan healthcare NHS, 2006:3).

Furthermore, the inhibitory effects on platelet aggregation and blood clotting make it useful in the prophylaxis of transient ischemic attacks, and of thrombosis and thrombo-embolism (Gibbon, 2003:397).

- *Adverse effects*

According to Feinberg (2000:45-46):

> aspirin is not a benign medication: it can cause serious side effects.

Adverse effects include shock requiring emergency medical attention, rashes, and gastro-intestinal bleeding.

Gibbon (2003:398) lists other adverse events such as: gastric irritation causing abdominal pain, nausea, vomiting and occult or overt mucosal bleeding; gastric erosion and acute haemorrhage if administered chronically; pseudo-allergic reactions such as bronchospasm, rhinitis, urticaria, angioedema and anaphylaxis-like shock; true hypersensitivity reactions; tinnitus and decreased hearing; impaired renal function and hepatotoxicity.

2.4.7.3 Ibuprofen

According to Burke *et al.* (2006) ibuprofen is the most frequently used non-steroid anti-inflammatory drug (NSAID) in the United States. There are many different NSAID's available, of which several can be purchased without prescription (Feinberg 2000:46).

The use of NSAID's has become increasingly popular because of the concern over opioid-related side effects (Buvanendran *et al.*, 2007:20).

- *Mechanism of action*

Ibuprofen is a propionic acid derivative, which is a non-selective cyclo-oxygenase inhibitor (Burke *et al.*, 2006).

According to Buvanendran *et al.* (2007:20) the primary site of action of non-steroidal anti-inflammatory drugs (NSAID's) is believed to be in the periphery although recent research indicates that central inhibition of cyclo-oxygenase (COX)-2 may also play an important role in modulating nociception.

NSAID's inhibit the enzyme cyclo-oxygenase which converts arachidonic acid to prostanoids, precursors of prostaglandins (Schug & Manopas, 2007:22). According to Hersh *et al.* (2000:506)

arachidonic acid is liberated from damaged cell membranes on exposure to the ubiquitous enzyme phospholipase A2.

The latest NSAID's do not acetylate COX but are reversible competitive inhibitors of the enzyme (Hersh *et al.*, 2000:506).

The non-selective blockade of the two isoenzymes, cyclo-oxygenase-1 and cyclo-oxygenase-2, by traditional NSAID's including aspirin, explains not only their effect with regard to analgesia, anti-inflammation and antipyresis, but also their characteristic side effects (Schug & Manopas, 2007:22).

- *Pharmacokinetics and administration*

According to Burke *et al.* (2006) *ibuprofen* is absorbed quickly, bound avidly to protein, and undergoes hepatic metabolism and renal excretion of metabolites. Ibuprofen has a half-life is roughly 2 hours. In experimental animals, ibuprofen and its metabolites readily cross the placenta (Burke *et al.*, 2006).

- *Clinical uses*

NSAID's are valuable in the management of pain, stiffness, inflammation, arthritis, and gout (Feinberg, 2000:46). According to Lichtman *et al.* (2006) the effectiveness of NSAID's is well established for initial treatment of mild to moderate pain and, when combined with an opioid, for treatment of moderate to severe cancer pain.

- *Adverse effects*

According to Schug and Manopas (2007:22) gastro-intestinal toxicity is a major problem when using non-selective NSAID's.

According to Tintinalli (2006) NSAID's do not produce physical dependence or tolerance. However, NSAID's have a ceiling effect, thus increasing the dose beyond a certain level does not increase the analgesic effect but may amplify toxic side effects (Tintinalli, 2006).

According to Ruane (2006:37) the downside of using NSAID's is their potential to cause gastro-intestinal toxicity.

According to Gibbon (2003:352) ibuprofen may cause gastric effects ranging from mild irritation to erosion, peptic ulceration and bleeding, as well as fluid and sodium retention. Hypersensitivity reactions are usually presents with bronchospasm, skin rashes, pruritus, urticaria and angioedema, and may be precipitated in patients who are sensitive to aspirin or other NSAID's. CNS effects of ibuprofen include headache, dizziness, drowsiness and depression. Other

adverse effects include toxic amblyopia, blurred vision and tinnitus (Gibbon, 2003:352).

2.4.7.4 Caffeine

Caffeine is commonly found in many analgesic products as an adjuvant (Goldstein, 2001:52).

Caffeine is a naturally occurring xanthenes derivative used as a CNS and respiratory stimulant, or as a mild diuretic. Caffeine is often combined with analgesics or with ergot alkaloids for the treatment of migraine and other types of headache (Anon, 2006).

According to Diamond *et al.* (2000:312) ibuprofen and caffeine administered together provides significantly greater analgesic effectiveness than either of the components alone.

- *Mechanism of action*

According to O'Brian (2007) caffeine mildly increases norepinephrine and dopamine release and enhances neural activity in numerous brain areas.

Many of caffeine's effects are believed to occur by means of competitive antagonism at adenosine receptors. Adenosine is a neuromodulator that influences a number of functions in the CNS. The mild sedating effects that occur when adenosine activates particular adenosine receptor subtypes, can be antagonised by caffeine (O'Brian, 2007).

- *Pharmacokinetics and administration*

Caffeine is almost completely absorbed in the GI tract (Goldstein, 2001:52). Caffeine absorption from the gastrointestinal tract is rapid and reaches 99% in humans in about 45 minutes after ingestion (Fredholm *et al.*, 1999:96).

Caffeine is absorbed from the digestive tract and is distributed rapidly throughout all tissues and easily crosses the placental barrier (O'Brian, 2007).

Caffeine is distributed rapidly to all body tissues and readily crosses the blood-brain and placental barriers and is distributed into breast milk. In adults, caffeine is partially metabolised in the liver via demethylation reactions dependent on the CYP-450 1A2 isoenzyme (Anon., 2006).

- *Clinical uses*

According to Granados-Soto and Castaneda-Hernandez (1999:67):

caffeine has been extensively used as an analgesic adjuvant, especially in formulations containing combinations with a variety of nonsteroidal anti-inflammatory drugs (NSAID's).

Caffeine has a synergistic effectiveness with analgesics. Although caffeine has dependence potential, the potential is low (Granados-Soto & Castaneda-Hernandez, 1999:67).

According to Fredholm *et al.*, (1999:104) caffeine is present in several analgesic preparations. Under conditions of pain, caffeine could have an indirect beneficial effect by elevating mood and clear-headedness.

- *Adverse effects*

Prolonged high intake of caffeine may lead to tolerance of some of the pharmacological actions and physical signs of withdrawal including irritability, lethargy, and headache may occur if intake is stopped abruptly (Sweetman, 2007).

Feinstein *et al.* (2000:457) concluded that the suspicions that caffeine combinations of analgesics might lead to dependence behaviour are not supported by data. Furthermore, there is no proof that caffeine-containing analgesics are more responsible for the developing of drug-induced headaches than other analgesics used alone, nor the singular use of migraine drugs. Furthermore, there is no proof that the withdrawal of caffeine-containing analgesics is of a higher extent than that of other headaches-inducing drugs (Feinstein *et al.*, 2000:457).

2.4.7.5 Diphenhydramine

Diphenhydramine is an antihistamine that has a pronounced sedative effect and is sometimes used as a hypnotic drug (Gibbon, 2003:439). According to Skidgel and Erdös (2006) diphenhydramine possess significant antimuscarinic activity and have a known tendency to induce sedation.

- *Mechanism of action*

H_1 antagonists, like diphenhydramine, inhibit most of the effects of histamine on smooth muscles, especially the constriction of respiratory smooth muscle (Skidgel and Erdös, 2006).

H_1 antagonists are competitive pharmacologic-antagonists at the H_1 receptor and has no effect on the release of histamine from storage sites (Trevor *et al.*, 2002:159).

The first-generation H_1 antagonists can both stimulate and depress the CNS. Central depression usually accompanies therapeutic

doses of the older H_1 antagonists. Diminished alertness, slowed reaction times, and somnolence are common manifestations. The ethanolamine (*e.g.* diphenhydramine) is particularly prone to cause sedation (Skidgel and Erdös, 2006).

- *Pharmacokinetics and administration*

According to Skidgel and Erdös (2006) the H_1 antagonists are well absorbed from the gastro-intestinal tract. Following oral administration, peak plasma concentrations are achieved in 2 to 3 hours, and effects usually last 4 to 6 hours; however, some of the drugs are much longer acting.

According to Skidgel and Erdös (2006) diphenhydramine, given orally, reaches a maximal concentration in the blood in about 2 hours, remains at about this level for another 2 hours, and then drops exponentially with a plasma elimination half time of about 4 to 8 hours. The drug is distributed widely throughout the body, including the CNS. Little is excreted unchanged in the urine; and it mostly appears as metabolites (Skidgel & Erdös, 2006).

- *Clinical uses*

H_1 antagonists have a reputable and respected place in the symptomatic treatment of a variety of immediate hypersensitivity reactions (Skidgel & Erdös, 2006). Furthermore, the central characteristics of some of the series are of therapeutic value for suppressing motion sickness or for sedation (Katzung & Julius, 2001:272).

The tendency of some H_1 receptor antagonists to produce somnolence has led to their use as hypnotics. H_1 antagonists, principally *diphenhydramine*, often are present in various proprietary remedies for insomnia that are sold over the counter (Skidgel & Erdös, 2006).

According to Katzung and Julius (2001:273) diphenhydramine and promethazine are actually more potent than procaine as local anesthetics.

- *Adverse effects*

According to Trevor *et al.* (2002:159) the most frequent side effect in the first-generation H_1 antagonists is sedation.

Although sedation may be a desirable adjunct in the treatment of some patients, it may interfere with the patient's daytime activities. Other central actions include dizziness, tinnitus, lassitude, in-coordination, fatigue, blurred vision, euphoria, nervousness, insomnia, and tremors. The next most frequent side effects involve

the digestive tract and include loss of appetite, nausea, vomiting, epigastric distress, and constipation or diarrhoea (Skidgel & Erdös, 2006).

2.4.7.6 Doxylamine succinate

- *Mechanism of action*

According to Gibbon (2003:52) doxylamine is an ethanolamine-type antihistamine with strong histamine-blocking activity and significant antimuscarinic action.

Doxylamine does not prevent the release of histamine, but competes with free histamine for binding at the H_1-receptor sites. Like other antihistamines, doxylamine competitively antagonises the effects of histamine on H_1-receptors in the gasto-intestinal (GI) tract, uterus, large blood vessels, and bronchial muscle. Blockade of H_1-receptors also suppresses the formation of oedema, flare, and pruritus that result from histaminic activity (Burke *et al.*, 2006).

First generation antihistamines such as doxylamine bind non-selectively to H_1-receptors centrally and peripherally. Thus, sedative effects are more likely to occur with first generation antihistamines, especially the ethanolamine group e.g. doxylamine, commonly promoted as a sleep-aid (Burke *et al.*, 2006).

- *Pharmacokinetics and administration*

Doxylamine is administered orally. The exact bioavailability of doxylamine has not been described; however, H_1-antagonists are generally well absorbed following oral administration (Burke *et al.*, 2006).

Peak plasma concentrations of doxylamine are reached 2 to 3 hours following oral administration and the duration of action is 3 to 8 hours. In general, antihistamines have a large volume of distribution (Burke *et al.*, 2006).

- *Clinical uses*

Doxylamine is used as an anti-emetic, alone or in conjunction with pyridoxine and dicyclomine. Because of its significant sedative effects, it has been used as such (Gibbon, 2003:52).

- *Adverse effects*

According to Burke *et al.* (2006) ethanolamine derivatives have greater anticholinergic activity than other antihistamines; therefore it produces side effects such as dry mouth, blurred vision, constipation and urinary retention.

2.4.7.7 Promethazine

- *Mechanism of action*

Prometazine is a non-selective antihistamine with considerable activity at other receptor sites, therefore it combines potent H1-antagonism with anti-emetic, anticholinergic and marked sedative activities and some hypotensive effects (Gibbon, 2003:500).

According to Skidgel and Erdös (2006) any of the first-generation H_1 antagonists tend to inhibit responses to acetylcholine that are mediated by muscarinic receptors. These *atropine*-like actions are adequately prominent in some of the drugs to be manifest during clinical usage. Promethazine has perhaps the strongest muscarinic-blocking activity among these agents and is amongst the most effective of the H_1 antagonists in fighting motion sickness (Skidgel & Erdös, 2006).

Some H_1 antagonists have local anaesthetic activity, and a few are more potent than procaine, but promethazine is particularly active. However, the concentrations necessary for this effect is a lot higher than those that antagonise histamine's interactions with its receptors (Skidgel & Erdös, 2006).

- *Clinical uses*

According to Skidgel and Erdös (2006), most drugs under this classification are H_1 antagonists and also possess considerable anticholinergic activity.

Promethazine is indicated for a variety of allergic conditions; the prevention of motion sickness, nausea and vomiting; sedation (particularly in children); in obstetrics and pre-operatively for its sedative, anti-emetic and antimuscarinic effects (Gibbon, 2003:500).

According to Skidgel and Erdös (2006) promethazine is useful in treating the nausea and vomiting succeeding chemotherapy or radiation therapy for malignancies.

- *Adverse effects*

According to Gibbon (2003:500) promethazine may cause drowsiness, dizziness, fatigue and in-coordination. Paradoxical stimulation with seizures, hallucinations and nervousness may occur, especially with high doses or if administered to children. The gastro-intestinal effects include nausea, vomiting and epigastric pain. Furthermore, anticholinergic effects such as dry mouth, blurred vision and urinary retention may occur. In rare cases, changes in heart rate and blood pressure, jaundice, photosensitivity, extrapyramidal symptoms, and haematological disturbances such as

agranulocytosis and leucopoenia have emerged in patients (Gibbon, 2003:500).

2.4.7.8 Phenobarbitone

- *Mechanism of action*

Phenobarbitone is a barbiturate, generally used as an anticonvulsant. It also has sedative and hypnotic characteristics but, as with other barbiturates, has been outdated by the benzodiazepines for these indications (Wikipedia, 2006d).

The mechanism by which phenobarbital inhibits seizures likely involves potentiation of synaptic inhibition through an action on the $GABA_A$ receptor (McNamara, 2006).

According to Trevor *et al.* (2002:206) barbiturates depress neuronal activity in the midbrain reticular formation, facilitating and prolonging the inhibitory effects of GABA and glycine.

- *Pharmacokinetics and administration*

According to McNamara (2006) oral absorption of phenobarbital is complete but somewhat slow: peak concentrations in plasma occur several hours after a single dose.

Phenobarbital is a lipid-soluble drug and is absorbed well from the gastro-intestinal tract, with good distribution to the brain. It is metabolised prior to elimination from the body, mainly by hepatic enzymes (Trevor *et al.*, 2002:206).

- *Clinical uses*

Phenobarbital is an effective agent for generalised tonic-clonic and partial seizures. Its efficacy, low toxicity, and low cost make it an important agent for these types of epilepsy. However, its sedative effects and its tendency to disturb behaviour in children have reduced its use as a primary agent (McNamara, 2006).

- *Adverse effects*

According to Noriston Ltd. (1995) phenobarbitone may cause sedation and respiratory depression. Allergic skin reactions, usually of the maculopapular type, or sometimes fixed-drug eruptions and photosensitivity may occur. Furthermore, hepatitis and cholestasis have been associated with barbiturate administration.

According to McNamara (2006) sedation, the most frequent undesired effect of phenobarbital is obvious to some extent in all patients upon initiation of therapy, but tolerance develops during chronic medication. Phenobarbital sometimes produces irritability

and hyperactivity in children, and agitation and confusion in the elderly.

2.4.7.9 Meprobamate

According to Charney *et al.* (2006) the properties of meprobamate bear some resemblance to those of the benzodiazepines, but the drug has a distinctly higher potential for abuse and has less selective anti-anxiety effects.

- *Mechanism of action*

Meprobamate is a carbamate derivative which is used as an anxiolytic drug (Wikipedia, 2006c).

The pharmacological properties of meprobamate resemble those of the benzodiazepines in a number of ways. Meprobamate can cause widespread depression of the CNS, but it cannot produce anaesthesia. Meprobamate appears to have a mild analgesic effect in patients with musculoskeletal pain, and it enhances the analgesic effects of other drugs (Wikipedia, 2006c).

- *Pharmacokinetics and administration*

According to Charney *et al.* (2006) meprobamate is well absorbed when administered orally and most of the drug is metabolised in the liver. The half-life of meprobamate may be prolonged during its chronic administration.

- *Clinical uses*

The clinical use of these agents has decreased markedly, and deservedly so. Nevertheless, some of them are useful in certain settings, particularly in hospitalised patients (Charney *et al.*, 2006).

- *Adverse effects*

According to Charney *et al.* (2006) ingestion of large doses of meprobamate alone can cause severe or even fatal respiratory depression, hypotension, shock, and heart failure.

The major unwanted effects of the usual sedative doses of meprobamate are drowsiness and ataxia; larger doses produce considerable impairment of learning and motor coordination and prolongation of reaction time (Charney *et al.*, 2006).

2.4.7.10 Orphenadrine

- *Mechanism of action*

According to Adcock Ingram Limited (1996) orphenadrine is a centrally acting muscle relaxant. It is an antimuscarinic agent related

to diphenhydramine, but without its hypnotic effect. It is used as a citrate to ease pain due to skeletal muscle spasm (Gibbon, 2003:366).

- *Clinical uses*

Orphenadrine is used in management of spasticity due to neuromuscular and musculoskeletal disorders and for the relief of painful muscle spasm (Adcock Ingram Limited, 1996).

- *Adverse effects*

Adcock Ingram Limited (1996) lists the adverse effects of orphenadrine as dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilating of the pupils with loss of accommodation and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition as well as reduction in the tone of motility of the gastro-intestinal tract leading to constipation. Sporadical vomiting, confusion, giddiness, staggering and spasms may occur.

2.4.7.11 Mephenesin

- *Mechanism of action*

Mephenesin is a centrally acting skeletal muscle relaxant used for symptomatic relief of painful muscle spasm (Gibbon, 2003:366).

- *Clinical uses*

According to Gibbon (2003:366) mephenesin is most often used for symptomatic relief of painful muscle spasm.

- *Adverse effects*

According to the Premier Pharmaceutical Company (PCC) (1969) mephenesin may produce lassitude, anorexia, nausea, vomiting and allergic reactions may occur. Mephenesin may enhance the effects of barbiturates and opioids.

2.4.7.12 Codeine phosphate and Dihydrocodeine

- *Mechanism of action*

According to Lichtman *et al.* (2006) codeine is a prodrug of morphine with a biotransformation of approximately 10%. The pharmacodynamic effects of codeine are the result of the production of its active metabolite morphine. Codeine can be used in combination with aspirin or paracetamol.

Dihydrocodeine is a weak opioid, which is effective for the relief of moderate pain of visceral origin (Lifespan healthcare NHS 2006:3).

- *Pharmacokinetics and administration*

Once absorbed, codeine is metabolised by the liver, and its metabolites are excreted primarily as inactive forms in the urine. A small fraction (approximately 10%) of administered codeine is *O*-demethylated to morphine, and free and conjugated morphine can be traced in the urine after therapeutic doses of codeine. Codeine has a remarkably low affinity for opioid receptors, and the analgesic effect of codeine is due to its switch to morphine. The half-life of codeine in plasma is 2 to 4 hours (Gutstein & Akil, 2006).

- *Clinical uses*

According to Wikipedia (2006a) the approved indications for codeine include cough, though its efficacy has been disputed, diarrhoea and moderate to severe pain.

- *Adverse effects*

Side-effects of codeine include nausea, vomiting and constipation (Lifespan healthcare NHS 2006:3). Oral doses greater than 200mg are associated with noteworthy side-effects of nausea and vomiting (Lichtman, 2006).

2.4.7.13 Propoxyphene

According to Lichtman *et al.* (2006):

> propoxyphene is about half to two thirds that of codeine.

Propoxyphene has been available as various formulations containing the HCl and napsylate salts, as well as in combinations with aspirin and other compounds (Fudula & Johnson, 2006:S41).

- *Adverse effects*

According to Lichtman *et al.* (2006) propoxyphene in high doses can cause cardiac conduction depression, convulsions, central nervous system depression, and respiratory depression.

2.4.7.14 Dextropropoxyphene HCl and Dextropropoxyphene napsylate

- *Mechanism of action*

According to Gutstein and Akil (2006) propoxyphene is structurally related to methadone and its analgesic effect resides in the D-isomer, D-propoxyphene (dextropropoxyphene).

> Dextropopoxyphene is a weak opioid analgesic used for treatment of mild to moderate pain. Dextropopoxyphene is particularly useful in individuals who are unable to metabolise codeine due to poor functioning of the enzyme CYP2D6, as its mechanism does not require CYP2D6 (Wikipedia, 2006b).

According to Gutstein and Akil (2006) propoxyphene binds mainly to μ-opioid receptors and produces analgesia and other central nervous system effects that are similar to those seen with other morphine-like opioids.

- *Pharmacokinetics and administration*

After oral administration, concentrations of propoxyphene in plasma reach their highest values at 1 to 2 hours (Gutstein & Akil, 2006). The average half-life of propoxyphene in plasma after a single dose is 6 to 12 hours, which is longer than that of codeine. In humans, the major route of metabolism is N-demethylation to form norpropoxyphene (Gutstein & Akil, 2006).

- *Clinical uses*

According to Gutstein and Akil (2006) propoxyphene is recommended for the treatment of mild-to-moderate pain. Given acutely, the commonly prescribed combination of 32 mg propoxyphene with aspirin may not produce more analgesia than aspirin alone, and doses of 65 mg of the hydrochloride or 100 mg of the napsylate are suggested (Gutstein & Akil, 2006). Propoxyphene is given most often in combination with aspirin or paracetamol. The wide popularity of propoxyphene is largely a result of unrealistic over-concern about the addictive potential of codeine (Gutstein & Akil, 2006).

- *Adverse effects*

It is likely that at high doses the incidence of side effects such as nausea, anorexia, constipation, abdominal pain, and drowsiness are similar to those of codeine (Gutstein & Akil, 2006).

2.4.7.15 Tramadol

Tramadol is a centrally acting analgesic of moderate potency with both opioid and non-opioid modes of action. It has a greatly reduced potential for sedation, respiratory depression and dependence compared to conventional opioids, making it an attractive choice for day surgery (Hammonds *et al.*, 2003:31).

- *Mechanism of action*

Tramadol is an out of the ordinary opioid structurally similar to tilidine, but apart from its morphine-receptor agonist action, it inhibits neuronal reuptake of serotonin and noradrenalin (Gibbon, 2003:390).

As a centrally acting analgesic, tramadol is a-typical because it produces analgesia through both mu opioid and monoamine actions (Epstein *et al.*, 2006:93).

According to Gutstein and Akil (2006) tramadol is a synthetic codeine analogue that is a weak μ-opioid receptor agonist. A fraction of its analgesic effect is produced by inhibition of uptake of norepinephrine and serotonin. In the treatment of mild-to-moderate pain, tramadol is as effective as morphine or meperidine.

- *Pharmacokinetics and administration*

According to Gutstein and Akil (2006) tramadol is 68% bioavailable after a single oral dose and 100% available when administered intramuscularly. Its affinity for the μ-opioid receptor is only 1/6000 that of morphine (Gutstein & Akil, 2006). However, the primary *O*-demethylated metabolite of tramadol is two to four times as potent as the parent drug and may account for part of the analgesic effect (Gutstein & Akil, 2006).

The compound undergoes hepatic metabolism and renal excretion, with an elimination half-life of 6 hours for tramadol and 7.5 hours for its active metabolite. Analgesia begins within an hour of oral dosing and peaks within 2 to 3 hours and the total duration of analgesia is about 6 hours (Gutstein & Akil, 2006).

- *Clinical uses:*

  Tramadol administered with NSAID's is valuable for relieving spastic visceral pain (Lichtman *et al.*, 2006).

- *Adverse effects*

Tramadol is contraindicated in patients taking monoamine oxidase inhibitors or serotonergic agents (Lichtman *et al.*, 2006).

Although tramadol has generally been regarded as safe, it,has been associated with numerous adverse drug reactions including seizures, respiratory depression, anaphylaxis, angioedema, bronchospasm, toxic epidermal necrolysis, and serotonin syndrome (Krantz *et al.*, 2005:498).

Gutstein and Akil (2006) list the common side-effects of tramadol as nausea, vomiting, dizziness, dry mouth, sedation, and headache.

> Respiratory depression appears to be less than with equivalent doses of morphine, and the degree of constipation is less than that seen after equivalent doses of codeine (Gutstein & Akil, 2006).

Tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors (Gutstein & Akil, 2006).

2.4.8 Classification of combination analgesics

Table 2.5 Classification of combination analgesics

	Combination	Indications
1	Acetylsalicylate/Paracetamol/Codeine phosphate/Caffeine	As an analgesic for conditions such as: tension headaches, toothache, earache, sinusitis, arthritis, post-surgical pain, fibrositis menstrual pains. As an antipyretic in colds, influenza and other virus infections. Febrile conditions in general.
2	Aspirin/Caffeine	Symptomatic relief of mild to moderate pain such as headaches, dysmenorrhoea, arthritis and headache.
3	Aspirin/Codeine phosphate	Symptomatic relief of mild to moderate pain such as headaches, dysmenorrhoea, pain in muscles and joints, dental pain, colds or flu and fever
4	Dextropopoxyphene/ Paracetamol	All conditions of moderate to severe pain.
5	Doxylamine succinate/Paracetamol /Codeine phosphate/Caffeine	Symptomatic relief of mild to moderate pain, pain associated with tension, and fever.
6	Ibuprofen/Codeine phosphate/ Paracetamol	Relief of mild to moderate pain with inflammatory origin (with or without fever).
7	Ibuprofen/Paracetamol	Indicated for fever and the relief of mild to moderate pain. Relief of headache from musculo-skeletal origin, muscular, menstrual and dental pain.
8	Paracetamol/Aspirin/Caffeine anhydrous	Symptomatic relief of mild to moderate pain such as headaches, dysmenorrhoea, pain in muscle- and joint-pain, dental pain, colds or flu and fever.
9	Paracetamol/Codeine phosphate/Vitamin C	Mild to moderate pain.

10	Paracetamol/Codeine phosphate	Relief of mild to moderate pain and fever, such as headaches, toothache and pain associated with colds and flu.
11	Paracetamol/Codeine phosphate/Prometasien HCl	Relief of mild to moderate pain, associated with fever. Post-operative pain, teething, dental pain, symptomatic relief in common childhood disease, measles, mumps, etcetera.
12	Paracetamol/Codeine phosphate/Caffeine/Meprobamate	Mild to moderate pain and fever, and pain associated with tension.
13	Paracetamol/Codeine phosphate/Meprobamate	Indicated for the relief of pain as well as tension related pain.
14	Paracetamol/Dextropopoxyphene/ Diphenhydramine HCl/Caffeine	Pain.
15	Paracetamol/Mephenesin	Generalised pain associated with tension.
16	Paracetamol/Orphenadrine citrate	Generalised pain and the relief of muscle spasm associated with acute painful musculo-skeletal conditions.
17	Paracetamol/Propoxyphene HCl	Indicated for the relief of mild to moderate pain.
18	Phenobarbitone/Paracetamol/Codeine phosphate/ Caffeine/Diphenhydramine HCl	Indicated for the relief of pain-tension states.
19	Propoxyphene HCl/Aspirin/Caffeine	For the relief of mild to moderate pain.
20	Paracetamol/Codeine phosphate/Caffeine anhydrous/Diphenhydramine HCl	Relieves fever and pain-tension states
21	Codeine phosphate/Ibuprofen	Mild to moderate pain including non-serious arthritic and rheumatic pain, soft tissue injuries such as sprains and strains, tendonitis, backache, nerve pain (neuralgia), migraine, headache, toothache

		and menstrual pain.
22	Paracetamol/Codeine phosphate/Meprobamate/Aspirin/Caffeine	Pain and pain associated with tension.
23	Paracetamol/Codeine/Phenobarbitone/Caffeine/Aluminium Acetylsalicilate/Chlorphenoxamine HCl	Analgesic: Tension headaches, toothache, earache, sinusitis, painful arthritic or rheumatic conditions, post-operative pain, neuralgia, menstrual pain. Antipyretic: colds, influenza, virus infections. General febrile conditions.
24	Paracetamol/Tramadol HCl	Indicated for the short-term treatment (i.e. three days or less) of mild to moderate acute pain.
25	Paracetamol/Codeine phosphate/Phenytoloxamine citrate/Caffeine	Treatment of muscle pain, neuralgia, pain following tooth extraction, dysmenorrhoea, sinus headaches, colds, influenza and fever.

2.4.9 Discussion of specific analgesic combinations

In this section, certain analgesic combinations wil be discussed.

2.4.9.1 Paracetamol/Aspirin/Caffeine anhydrous

A number of OTC analgesic/antipyretic agents available include combinations of aspirin and paracetamol. Caffeine is also normally included in these combinations (Hersh *et al.*, 2000:509).

The original rationale for combining aspirin and paracetamol was based on the idea of:

> cross firing, which is enhancement of efficacy by administering drugs that produce the same effect but by different mechanisms (Hersh *et al.*, 2000:509).

According to Hersh *et al.* (2000:509) analgesic improvement beyond that obtained with therapeutic doses of aspirin or paracetamol alone can evidently be demonstrated when these drugs are combined with narcotic analgesic ingredients such as codeine, hydrocodone, or oxycodone. However, the same additive effect is not obtained when aspirin is combined with paracetamol (Hersh *et al.*, 2000:509).

The advantage of the aspirin/paracetamol combination is seen only when caffeine is a part of the combination (Hersh *et al.*, 2000:509).

2.4.9.2 Paracetamol/Codeine phosphate/Caffeine anhydrous/Diphenhydramine HCl

The combination of paracetamol, codeine phosphate, caffeine anhydrous and diphenhydramine HCl is sometimes known as a "convenience combination" (Hersh *et al.,* 2000:511).

According to Hersh *et al.* (2000:510) convenience combinations normally contain aspirin, paracetamol, or ibuprofen plus a another ingredient such as a nasal decongestant, an antihistamine, a cough suppressant, or an antacid to treat other symptoms associated with pain and fever, such as those of the common cold, sleeplessness, coughing, or acid indigestion.

However, these combinations can only be valuable if more than two symptoms are present. Unfortunately these combinations are frequently misused by the general public, leading to unnecessary exposure to one or more of the constituents. The other ingredients will also increase the potential for side effects without increasing analgesic efficacy (Hersh *et al.*, 2000:511).

2.4.9.3 Paracetamol/Codeine phosphate

According to De Craen *et al.* (1996:324) paracetamol-codeine preparations produce a significant increase in analgesia compared with paracetamol alone. Multidose studies done by De Craen *et al.* (1996:324) show an increased occurrence of side effects with paracetamol-codeine. Thus for occasional pain relief a paracetamol-codeine combination might be suitable, but frequent use increases the incidence of side effects.

> Therapeutic doses of paracetamol do not influence the pharmacokinetics and metabolism of codeine and codeine has no effect on the metabolism and clearance of paracetamol (De Craen *et al.*, 1996:324).

2.4.9.4 Paracetamol/Tramadol HCl

The orally administered fixed combination tablet of tramadol and paracetamol provides efficient analgesia in patients with moderate to severe acute pain and those with chronic pain conditions characterised by irregular exacerbations of pain (McClellan & Scott, 2003:1079).

2.4.10 Toxic effects of combination analgesic drugs

Because of the relatively unrestricted access to OTC analgesics, many consumers believe that the medications are innocuous and therefore they often do not inform their doctors when they use them.

As a result, consumers may purchase and use OTC analgesics without considering their contraindications, precautions and drug interactions (Pigeon *et al.*, 2006:576).

According to Hersh *et al.* (2000:521) the adverse drug reactions associated with the use of aspirin, paracetamol, the more recent NSAID's and their combinations can normally be grouped according to three target organ systems: the gastro-intestinal-, renal-, and hepatic-systems. When assessing the possible side effects of these drugs, it is essential to distinguish between three different clinical situations: (1) chronic administration of these drugs (usually as prescribed), (2) OTC patterns of use; and (3) cases of deliberate and unintended overdose (Hersh *et al.*, 2000:522).

Clearly, it cannot be assumed that the side effects related with a non-prescription drug misuse are necessarily comparable in incidence and frequency to those associated with prescription use of the same drug (Hersh *et al.*, 2000:522).

According to Driesens *et al.* (2003:66) three significant issues must be addressed when you want to determine whether combination analgesics play a role in analgesic nephropathy.

- Firstly, a fundamental link between the **combination** itself and nephrotoxicity has never been sufficiently documented (Driesens *et al.*, 2003:66). The origin of the nephrotoxicity is most likely the analgesic mechanism, i.e. the antagonism to prostaglandins which is the most potent prostaglandin-antagonists and the non-steroidal anti-inflammatory drugs, whether used in **combination** or singly, also most frequently cause renal pathology (Driesens *et al.*, 2003:66).
- Driesens *et al.* (2003:66) states that the safety of combination analgesic drugs in contrast with that of single substances,

  > is intimately bound up with the advantages of the former with respect to both activity and the activity-side-effects ratio.

2.4.10.1 Paracetamol poisoning

According to Osborne and Bryant (2003:48) paracetamol is the most regular pharmaceutical agent accountable for poisonings reported in the United States in 2002. Unfortunately, unintentional paracetamol poisoning is common.

Paracetamol overdosage is predominantly dangerous as it may cause severe or sometimes fatal hepatic damage (Lifespan healthcare NHS, 2006:3).

According to the FDA (2004:1):

> paracetamol is chemically a para-aminophenol derivative that is also the active metabolite of the analgesic drug phenacetin.

Its efficiency as an antipyretic agent has been credited to its effect on the hypothalamic heat centre, whilst its analgesic effectiveness is due to its capability to raise the pain threshold. Furthermore, paracetamol's ability to cause fulminant hepatic failure in acute intentional overdose situations or when used in combination with alcohol is also well known (FDA, 2004:1).

The FDA (2004:1) have established that there are four factors which have resulted in potentially fatal or life threatening unintentional paracetamol overdoses in adults:

- failure by consumers to identify the possible harm caused by exceeding the recommended dose of the ingredients enclosed in over-the-counter drug products (FDA, 2004:1);
- the wide variety and accessibility of both over-the-counter and prescription drug products that contain paracetamol (FDA, 2004:1);
- the lack of consumer consciousness for the potential to develop serious adverse events from taking two or more different products containing paracetamol concurrently (FDA, 2004:1);
- the failure of prescription container labels to list paracetamol as an ingredient (FDA, 2004:1);

Furthermore the FDA (2004:1) has identified four factors which have resulted in unintentional paracetamol overdoses in children:

- administering the wrong paediatric paracetamol formulation [i.e., substituting the concentrated infant drops (80mg/0.8ml) for the less concentrated children's suspension (160 mg/5 ml)] (FDA, 2004:1);
- administering the adult instead of the age-appropriate children's dosage (FDA, 2004:1);
- incorrectly calculating the weight-appropriate dose of paracetamol (FDA, 2004:1);
- using the wrong dosing device (e.g., tablespoon instead of teaspoon, dropper versus syringe) (FDA, 2004:1).

Due to the dangers of paracetamol poisoning, the Medicine Control Council requires that the following information appear on all paracetamol containing products:

> In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic,

the nearest doctor, hospital or Poison Centre must be contacted immediately.

Furthermore the sentences:

dosages in excess of those recommended may cause severe liver damage

and

do not exceed the recommended dose,

should appear on the package insert (MCC, 2004:1).

According to the Medicines Control Council (2004) the known symptoms of overdosage and particulars of its treatment are:

- Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.
- Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.
- Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.
- Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.
- Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

According to Burke *et al.* (2006) paracetamol overdose is a medical emergency and can cause liver damage which occurs in:

90% of patients with plasma concentrations of paracetamol greater than 300 µg/ml at 4 hours or 45 µg/ml at 15 hours after the ingestion of the drug.

Minimal hepatic damage can be anticipated when the drug concentration is less than 120 µg/ml at 4 hours or 30 µg/ml at 12 hours after ingestion. The nomogram provided in fig. 2.5 relates the plasma levels of paracetamol and time after ingestion to the predicted severity of liver injury.

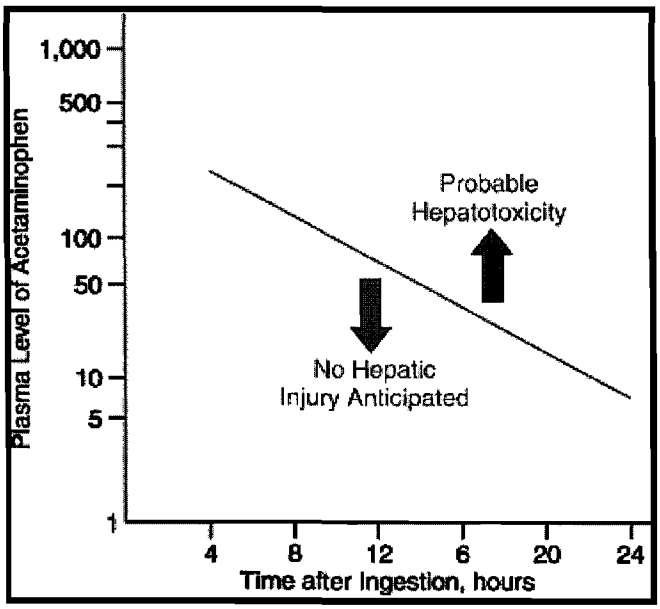

Figure 2.6 The relationship of plasma levels of paracetamol and the time after acute indigestion to hepatic injury (Burke *et al.*, 2006).

Early diagnosis and treatment of paracetamol overdose is essential to optimise the result. Activated charcoal, if given within 4 hours of ingestion, decreases paracetamol absorption by 50% to 90% and is the preferred method of gastric decontamination (Burke *et al.*, 2006).

2.4.10.2 Dangers associated with non-selective NSAID's (including aspirin) use

OTC analgesic NSAID are widely used, frequently taken inappropriately and potentially dangerously, and are generally believed to be safe (Wilcox *et al.*, 2005:2223).

According to the Medicines Control Council (2006b) it is very hazardous to use two or more NSAID's concurrently because it could result in an increase in adverse effects. They advocate the use of the lowest effective dose for the shortest possible duration of treatment.

Other warnings which are required to appear on all NSAID package inserts include:

- Caution is necessary in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy (MCC, 2006b:2).
- The product is contraindicated in patients with a history of gastrointestinal bleeding or perforation related to prior NSAID's usage, as well as a recurring ulcer/haemorrhage/perforations (MCC, 2006b:2).
- Treatment should be stopped when gastrointestinal bleeding or ulceration occurs (MCC, 2006b:2).
- NSAID's should be given with care to patients with a history of gastrointestinal disease as the condition may be exacerbated (MCC, 2006b:2).
- Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolyis have been reported. NSAID treatment should be stopped at the first manifestation of skin rash, mucosal lesions, or any other sign of hypersensitivity (MCC, 2006b:2).

In the elderly, the following dangers exist:

- The elderly have an increased frequency of adverse reactions to NSAID's, especially gastrointestinal bleeding and perforation which may be fatal (MCC, 2006b:2).
- The risk of gastrointestinal bleeding or perforation is higher with increasing doses in patients with a history of ulcers (MCC, 2006b:2).

2.4.10.3 Contraindications and precautions

Pain and discomfort in everyday life are often treated with OTC analgesic drugs which are remarkably safe, but serious side effects can occur (Abbott & Fraser, 1998:13).

According to Hersh *et al.* (2000:527) the product information that accompanies OTC analgesics includes numerous warnings, but the most important contraindications to their use is caused by prolonged prescription therapy at high doses.

When package insert instructions for dosage and duration of OTC therapy are followed by patients, side effects are rarely encountered. However, even low-dose and short-duration exposure to some of the

OTC analgesics may place certain patients at unnecessary risk (Hersh *et al.*, 2000:527).

The toxicities associated with OTC analgesics include renal and hepatic disease, GI ulceration, and bleeding disorders (Pigeon *et al.*, 2006:576).

According to Hersh *et al.* (2000:527) the patient information given with OTC analgesics specifically lists three warnings:

- aspirin intolerance/cross-sensitivity,
- pregnancy,
- and concomitant alcohol use.

2.5 The usage of analgesics worldwide

2.5.1 South Africa

According to Raff (2002:34) South African doctors have the largest choice of combination analgesic preparations available on prescription. These preparations contain various combinations of the analgesics paracetamol, codeine, propoxyphene, and meprobamate. These may be supplemented with non-steroidal anti-inflammatory agents (NSAID's), and many other additives including caffeine, antihistamines, pemoline, amino acids, and vitamins.

In a study done by Truter (1998:92) it was established that one-third (33.1%) of all prescriptions, from four metropolitan areas in South Africa, for central nervous system (CNS) drugs were for analgesics, of which combination analgesics represented 81.2% of the total number.

Meyers *et al.* (2003:367) identified that despite the abuse potential of OTC and prescription medications documented by prospective studies of the general populations in countries like the USA, there is little research describing the prevalence of OTC/prescription medicine misuse in South Africa.

2.5.2 Finland

In Finland, for example, analgesics constitute the leading selling group of over-the-counter (OTC) medicines (Turunen *et al.*, 2005:374).

According to Turunen *et al.* (2005:374), NSAID's are the most frequently used drugs for the treatment of pain in Finland, although during the recent years, the consumption of paracetamol and opioids has increased.

In the year 2002, the best-selling products for pain management in Finland were ibuprofen, paracetamol, a combination of codeine and paracetamol, rofecoxib, naproxen, and other NSAID's. Fifty-four percent of ibuprofen was sold over the counter, and it accounted for most of the non-prescribed analgesic consumption. NSAID's, both prescribed and OTC preparations may have serious adverse effects (Turunen *et al.*, 2005:374).

2.5.3 United States of America

According to Turunen *et al.* (2005:374) in the United States, reported as 1 week's prevalence of use, the three most frequently used drugs were analgesics.

Over-the-counter (OTC) analgesics, cough and cold products are the most frequently used medications in the United States. Nearly 80% of American adults take an OTC analgesic at least once a week (American academy of family physicians, 2002).

In the United States, codeine is regulated by the Controlled Substances Act. It is a Schedule II controlled substance for pain-relief products containing only codeine or more than 90 mg per dosage unit. In combination with aspirin or paracetamol it is listed as Schedule III or V, depending on formula (Wikipedia, 2007d).

Orphenadrine is also available mixed with aspirin, paracetamol, caffeine, and/or codeine in many places. All orphenadrine preparations require a prescription in the United States (Wikipedia, 2007d).

2.5.4 United Kingdom

In the United Kingdom (UK) analgesics that can be purchased without prescription are paracetamol, aspirin, and ibuprofen, with some products also containing low dose opiates such as codeine phosphate (Porteous *et al.*, 2005:79).

In September 1998, legislation was introduced in the UK to reduce the size of packs of paracetamol and salicylates sold over the counter. The legislation significantly reduced the size of overdoses, with consequent reductions in morbidity and mortality. Clearly the legislation can not prevent an individual intent on obtaining large supplies from purchasing through multiple outlets, but self poisoning is, however, often impulsive and involves tablets readily available in households (Hawton *et al.*, 2003:1156).

Other countries that have addressed this problem, such as France and Ireland, have had greater reductions in pack sizes than the UK (Hawton *et al.*, 2003:1156).

There is a limit on the amount of ibuprofen which can be bought over the counter in a single transaction in the UK; this being 2 packs of 16 x 200 mg or 1 pack of 8 or 16 x 400 mg, the latter being far less common for over-the-counter sales (Wikipedia, 2007d).

2.5.5 Europe

Codeine is listed under the narcotics & controlled substances law in Germany, Switzerland and in Austria in categories corresponding to their classification under the Single Convention on Narcotic Drugs. Dispensing of products containing codeine and similar drugs (dihydrocodeine, nicocodeine, benzylmorphine, ethylmorphine & c.) generally require a prescription order from a doctor or the discretion of the pharmacist (Wikipedia, 2006a).

2.5.6 Sweden

In a study done by Antonov and Isacson (1998:492) it was established that Swedish women reported use of analgesics both with and without prescriptions to a larger extent to that of men. A percentage of 12.2% women reported prescription analgesic use and 30.4% reported nonprescription analgesic use while corresponding proportions among men were 7.2% and 20.0%, respectively.

2.5.7 Australia and New Zealand

According to Wikipedia (2006a) codeine is regulated in Australia and New Zealand, however, it is available without prescription in combination preparations from licensed pharmacists in doses up to 15 mg/tablet.

2.5.8 Canada

According to Wikipedia (2006a) codeine is regulated in Canada but is also available without prescription in combination preparations from licensed pharmacists in doses up to 8 mg/tablet .

In Canada, codeine can only be sold over the counter in combination with 2 or more ingredients, which has resulted in the prevalence of aspirin, codeine, caffeine, and similar combinations using paracetamol rather than aspirin (Wikipedia, 2006a).

Orphenadrine preparations are available over the counter in Canada (Wikipedia, 2007d).

2.5.9 Hong Kong

According to Wikipedia (2006a), codeine is regulated under Schedule 1 of Hong Kong's Chapter 134 *Dangerous Drugs Ordinance*. It can only be used legally by health professionals and for University research purposes. The substance can be given by pharmacists under a prescription. Anyone who supplies the substance without prescription can be fined $10000 (HKD). The penalty for trafficking or manufacturing the substance is a $5,000,000 (HKD) fine and life imprisonment. Possession of the substance for consumption without license from the Department of Health is illegal with a $1,000,000 (HKD) fine and/or 7 years of jail sentence.

2.6 Analgesics abuse

2.6.1 Introduction to drug abuse

Fudula and Johnson (2006:S40) explained that medication abuse can take place under an assortment of circumstances. For example healthcare professionals who have direct admission to the medication and by patients for whom the medication has been prescribed, but who use it recreationally for other than its intended therapeutic purposes. Additionally, individuals other than the patients for whom the medication has been prescribed, may misuse it.

According to Molea and Augustyniak (2005:187) drug addiction is:

> a chronic relapsing brain disorder characterised by neurobiological changes that lead to a compulsion to take a drug and loss of control over drug intake.

It is important to understand the difference between abuse, dependence and addiction.

- *Abuse*

According to Molea and Augustyniak (2005:189) the term abuse refers to:

> use in a manner other than what is socially acceptable.

This may include using a medication:

> recreationally, in larger amounts, in greater frequency, for different indications, or by different routes, usually resulting in adverse consequences (Molea & Augustyniak, 2005:189).

- *Dependence*

According to Molea and Augustyniak (2005:187) dependence is a physiological process, which is a predictable event in the prescription of opioids, benzodiazepines, barbiturates, and, to some degree, stimulants. Physiological dependence is not necessarily an addiction.

> Dependence is dose-, time-, and potency-related and may result in tolerance (to side effects and to therapeutic effects) and withdrawal (Molea & Augustyniak, 2005:189).

- *Addiction*

According to Patt (2006) addiction is:

> a complex psychobehavioral syndrome characterised by overwhelming involvement in the acquisition and nonmedical use of a substance despite the threat of physiologic and/or psychological harm.

According to Molea and Augustyniak (2005:189):

> addiction is a further evolution of behaviour, with loss of control and an obsessive-compulsive pattern of use that rises to the level of a primary illness.

Physiological homeostatic changes leading to tolerance, withdrawal, or sensitisation may occur, and cognitive changes are common at this stage (Molea & Augustyniak, 2005:189). Miguel (2005:221) states substance abuse and psychopathology is frequently present in pain suffering patients and often complicates pain treatment.

2.6.2 Scheduling status of analgesics and combination analgesics in South Africa

The different combination analgesic medicine items available on the South African market has varying scheduling status, depending on the individual active ingredients scheduling status and dosage. The active ingredient scheduling status for certain combination analgesic ingredients is discussed in Table2.6. Scheduling status varies from schedule 0 for instance Compral® headache tablets, which contains 100mg paracetamol, 400mg aspirin and 30mg caffeine anhydrous, to schedule 5 status for instance Lentogesic® capsules, Synap Forte® tablets, Stopayne® tablets etcetera. The scheduling status of all medicine items included in this study is indicated in chapter 5.

Table 2.6 Active ingredient scheduling status for certain combination analgesic ingredients (adapted from S.A. 2003a).

Active ingredient	Schedule (S)	Exeptions
Paracetamol	S1	Paracetmol is Schedule 0: - in tablets or capsules each containing 500 mg or less of paracetamol, - in individually wrapped powders or in sachets containing 1000 milligrams or less of paracetamol. - when packed in a primary pack containing not more than an aggregate of 12,5 g of paracetamol in such tablets, capsules or individually wrapped powders or sachets; - packed in blister strip packaging or in containers with child-resistant closures; - in liquid or syrup dosage form containing 120 milligrams or less of paracetamol per 5ml or in pediatric dosage form (drops) containing 120 milligrams or less paracetamol per 1,2 ml; - when packed in a primary pack containing not more than 100 ml in the case of the liquid or syrup dosage form containing 120 milligrams or less paracetamol per 5ml; - the primary pack is labeled with the following boxed warning, placed prominently on at least the main panel of the immediate container label and outer label (carton): CONTAINS *PARACETAMOL- READ THE PACKAGE INSERT.*
Aspirin	S0	None
Codeine	S2	- preparations and mixtures when compounded with one or more therapeutically active substances and containing 20 mg or less of codeine (calculated as base) per dosage unit and liquid oral preparations and mixtures containing 20 mg or less dihydrocodeine (calculated as base) per 5 ml dosage unit (S6).
Ibuprofen	S2 S2	Ibuprofen is S2 when used in oral medicinal preparations: - where the recommended daily dose for adults does not exceed 1,2 and that for children up to and including the age of 12 years does not exceed 20 mg per kilogram

		of body weight; - the emergency treatment of acute gout attacks; - when intended for the treatment of post traumatic conditions such as pain, swelling and inflammation, for a maximum period of 5 days; except when intended for treatment of inflammatory joint disease (S3).
Mefenamic acid	S2	Mefenamic acid is S3 when: - intended for the treatment of post traumatic conditions such as pain, swelling and inflammation, for a maximum period of *5* days; - preparations containing mefenamic acid as the only therapeutic active substance, when intended for the treatment of primary dysmenorrhoea where the maximum daily dose is *500* mg 3 times a day and the maximum treatment period is 3 days.
Promethazine	S2	Promethazine is S5 in preparations and mixtures when intended for use as an antihistamine, for application to the skin and when intended specifically for the treatment of travel sickness.
Phenobarbitone	S3	Phenobarbital is S5 preparations and mixtures containing not more than 90 milligrams of phenobarbital per minimum recommended or prescribed dose when intended for continued use in epilepsy.
Dextropropoxyphene	S5	Dextropropoxyphene is S6 in preparations and mixtures for oral use containing not more than 135 milligrams of dextropropoxyphene, calculated as the base, per dosage unit or with a concentration of not more than 2,5 percent in undivided preparations.
Tramadol	S5	None
Meprobamate	S5**	None

** Specified Schedule

2.6.3 Patient characteristics of prescription drug abusers

There are several characteristics pin-pointing patients who abuse prescription drugs, when they network with the medical care system. These characteristics include escalating-use patterns, drug-seeking behaviour, doctor shopping, and the use of "scams" to maintain and increase their supply of drugs (Molea & Augustyniak, 2005:189).

According to Molea and Augustyniak (2005:187) a more helpful way to approach the topic of such demanding patients may be to think first about behaviours that are suggestive of drug-seeking patients,

and then think about some of the psychological and social issues that may cause that behaviour to manifest. Examples of demanding patient behaviours that may point to substance abuse (Molea & Augustyniak, 2005:189) include:

- numerous complaints concerning multiple body systems;
- unclear and shifting complaints;
- bombardment of complaints;
- dependent, clinging behaviour;
- unwarranted concern about minor symptoms;
- high utilisation of health care services;
- difficult, domineering, manipulative personality style;
- openly hostile even when not invoked;
- idealistic expectations of cure;
- raises problems right at end of visit;
- disobedient; and
- confused, non-specific.

2.6.4 Over-the-counter (OTC) analgesic abuse

Over-the-counter (OTC) drugs are those that can be safely self-administered by the public, without a physician's prescription or supervision (Hersh *et al.*, 2000:503). The fact is that, even though these medications are a significant tool for consumers to use in treating their own minor illnesses, these drugs are safe only if used according to package directions (ASA, 2006).

In a South African study done by Myers *et al.* (2003:367) it is said that health researchers have neglected the issue of OTC and prescription medicine abuse. They established that OTC/ and prescription analgesics are two of the most widely misused classes of medicines. They calculated that OTC/prescription analgesic were the second most frequently reported class of medicines misused in Cape Town, of which codeine-containing analgesics are the more commonly misused analgesics.

Truter and Kotze (1996:1394) stated that general practitioners attempt to under normal conditions, provide analgesia by orally administered medication, selecting from the multitude of prescription and over-the-counter products that are obtainable in pharmacies. When administered in the proper setting and used sensibly, these agents are very safe. According to Turunen *et al.* (2005:378) regular

use of prescribed analgesics can be considered reasonable as long as it aims to ease a medical condition evaluated by a physician.

Turunen *et al.* (2005:378) further stipulates that unsupervised long-lasting use of OTC analgesics with no suitable medical examinations and diagnosis can suppress symptoms caused by a condition that might require urgent medical attention. Truter and Kotze (1996:1394) also add that analgesics have concealed dangers when used chronically and in higher dosages than those indicated.

Unsupervised use of over-the-counter drugs that include paracetamol, aspirin or ibuprofen offers clinical challenges to both patient and health care providers. Combine these often secret over-the-counter medication incidents with prescription medications, of which many include comparable combination ingredients, and the potential for a therapeutic accident may precipitate (Barkin, 2001:434).

According to Turunen *et al.* (2005: 379) OTC analgesics may have serious adverse effects, especially if the suitability of the pharmaceutical agent for the individual has not been established. Overlapping use of both prescribed and OTC analgesics increase the risk for side effects due to possible interactions and overdosing.

The American Society of Anaesthesiologists (ASA, 2006) is worried about the abuse of over-the counter medications, because they established that there seems to be a public perception that if a drug can be purchased without a prescription, then it cannot cause any real damage.

According to Elseviers and De Broe (1996:S48) analgesic abuse can be defined as

> a daily consumption of analgesic mixtures over a several-year period.

Abuse of single analgesics is rare, it has been clearly confirmed that abusers prefer analgesic combinations (Elseviers and De Broe, 1996:S48).

Bond and Novak (1995:177) established that non-narcotic analgesics – aspirin and other non-steroidal anti-inflammatories and paracetamol – were the primary agents in 16% of the 405 suicide attempts that involved pharmaceuticals of which paracetamol would represent about half of non-narcotic analgesics, or 8% of the total.

According to Driesens *et al.* (2003:66) abuse, should be recast in a broader context. The vital element here is not the analgesic drug but rather the personality of the user in combination with a more or less

demanding environment in which a wide assortment of drugs and stimulants are obtainable and taken for better "coping".

Driesens *et al.* (2003:66) suggests that analgesics abuse can be prohibited by more accessible information (i.e. social medicine). In a broader perspective, man experiences substantial difficulty adapting to the extensive social, technological and ideological changes of recent decades and this change contributes in no small measure to the analgesics dilemma.

According to Hersh *et al.* (2000:524) OTC medications and their possibility for accidental or deliberate overdose is a vital public health concern. Aspirin overdose remains a relatively common means of attempting suicide in young adults.

Paracetamol is an extraordinarily safe agent when used at therapeutic dosages. However, its deadly potential when taken in overdose is often underestimated, particularly by adolescents. An attention-getting suicidal gesture often becomes a tragic truth (Hirsch *et al.*, 2000:525).

2.6.5 Opioid addiction

According to Fudula and Johnson (2006:S40) non-medical abuse of prescription opioids is not a new phenomenon, but such abuse has been growing in recent years.

Compton and Volkow (2006:103) writes that the abuse of, and addiction to opioid analgesics has emerged as a major problem for the United States in the past decade and has worsened over the past few years. They explain that the increases in abuse of these opioids appear to reflect, in part, changes in medication prescribing practices, changes in drug formulations as well as relatively easy access via the Internet.

The medications most often implicated in prescription drug abuse are opioid analgesics, sedative hypnotics, and stimulants. Because they are exposed to these drugs, patients with acute or chronic pain are at increased risk of addiction co-morbidity (Molea & Augustyniak, 2005:187).

Beers and Berkow (2006) defines opioid dependence as a strong psychological dependence manifested in an overpowering desire to continue taking opioids, the development of tolerance so the dose must be increased to obtain the original affect. And physical dependence that increases in intensity with bigger dosage and duration of use. Physical dependence necessitates continuous use of the same opioid or an associated one to avoid withdrawal.

Withdrawal of the drug or administration of an antagonist precipitates a typical, self-limited withdrawal syndrome (Beers and Berkow, 2006).

The National Institute on Drug Abuse (NIDA, 2006) includes codeine, morphine and other opioid analgesic in its list of generally abused drugs.

According to NIDA (2006) commercial/street names for codeine include:

> captain cody, schoolboy (with glutethimide), doors and fours, loads and pancakes and syrup.

It can either be injected or swallowed. Intoxication effects of codeine consist of pain relief, euphoria, drowsiness / nausea, constipation, confusion, sedation, respiratory depression and arrest, tolerance, addiction, unconsciousness, coma and death (NIDA, 2006).

According to McQuay (1999:2229) what happens when opioids are given to someone in pain is different from what happens when they are given to somebody who is not in pain. Feinberg (2000:47), states that opioids have gained a level of acceptance for chronic pain management, although their use for non-cancer-related pain remains controversial due to fears of reliance and addiction. McQuay (1999:2229) states that the diversity in opioid pharmacology between individuals with or without pain applies to addiction.

Addiction is unlikely when opioids are used for chronic pain, but dependence or tolerance can occur (Feinberg, 2000:47). According to McQuay (1999:2229) the drug seeking synonymous with drug addiction does not occur in patients after pain relief with opioids after childbirth, operations or a myocardial infarction. Drug addicts are not in pain. The political message is that the medical use of opioids does not create drug addicts, and restrictions on this medical use is an inconvenience for patients.

Beers and Berkow (2006) states that acceptance and physical dependence on opioids (natural or synthetic) develops rapidly. Feinberg (2000:47) adds that chronic patients who develop tolerance or dependence are not considered to be addicted, because they are using opioids for medically prescribed conditions and have evidence of advantage with medication use. Although opioid analgesics are sporadically associated with adverse drug events, the biggest problem is their inappropriate use (Tintinalli, 2006).

The Medicines Control Council (2006a:40) recognises the dependence potential of opioids and requires that the following warning appear on the immediate container label, the outer label and the package insert of all codeine-containing products:

> Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction.

- *Methods used to limit diversion and abuse of opioid medications*

According to Fudula and Johnson (2006:S40) numerous methods have been used and new methods are continuously developed in an attempt to limit diversion and abuse of opioid medications. These may include such straight forward measures as education of health professionals, increasing regulatory controls (e.g. drug scheduling), and restricting medicinal use to a medically supervised (e.g. hospital) situation. More complicated methods include the development of multifaceted dosage forms that oppose tampering, and the use of radio frequency identification (RFID) technology to track medications through the supply chain.

2.6.6 Meprobamate overdosage

Meprobamate is a mild sedative-hypnotic drug used in therapy since the 1950s (Gailliard *et al.*, 1997:173). An overdose of this drug, even when taken alone, produces intoxication that is often severe and occasionally life-threatening. This carbamate is sometimes implicated in accidental or suicidal overdoses, where hemodynamic events such as dramatic acute circulatory failure characterise the principal causes of death. Moreover, meprobamate is widely known in France and particularly in use in suicide attempts (Gailliard *et al.*, 1997:173).

In a study conducted by Gailliard *et al.* (1997:177) it was documented that among 124 self-provoked pharmaceutical overdoses, meprobamate was detected 37 times and was quantified at appropriate levels to explain the fatality in 19 cases. Although neuroleptics and tricyclic antidepressants represent the main pharmacological classes responsible for cause of death, meprobamate as a molecule is the most prevalent. In fact this drug alone represented 15.3% (19 cases out of 124) of the deaths imputable to acute toxic self-poisoning. Meprobamate was followed by dextropropoxyphene, which was responsible for 12 fatalities.

2.6.7 Internet drug/formulation tampering with codeine preparations.

In a study conducted by Cone (2006:S31) it is stated that the motives for drug/formulation tampering appear to be enhanced drug effects and a faster onset of action. Formulation tampering may allow quicker drug delivery by the intended route, access to a higher dose, changes to alternate faster routes of administration, and separation of undesirable ingredients.

When focusing on codeine preparations, Cone (2006:S31) described the following:

- Typical OTC codeine contains 8 mg of codeine phosphate in combination with 325 mg of paracetamol. Prescription doses range from 15 to 60 mg and are formulated as codeine sulfate (only) and codeine phosphate in combination with other OTC actives and together with butalbital and promethazine (Cone, 2006:S31).
- Recreational codeine users generally administer much higher doses than available by OTC or prescription. An internet site, *Codeine Information*, as quoted by Cone (2006:S33) indicates:

  > The average recreational dose for non-tolerant adult users starts at about 200 mg. Although effects start from 30 to 60 mg, some people may experience euphoria only in higher doses, usually >150 mg (Cone, 2006:S31).

- Legitimate concerns abound on the internet about recreational use of codeine in combination with other active ingredients such as paracetamol (potential liver damage), aspirin (gastrointestinal bleeding), caffeine, and ibuprofen. It is a common belief on the internet that companies formulate codeine in combination with other active ingredients such as paracetamol to prevent excessive use, as seen on the site *Codeine FAQ*, and quoted by Cone (2006:S33).
- Recreational codeine users frequently attempt to purify codeine formulations by removing paracetamol, aspirin and other ingredients, thereby circumventing potential toxicity from these substances. A variety of "Cold Water Extraction" recipes as provided on the sites *ADH-The Page*, *Neonjoint.com* and *Codeine.50g.com* (Cone, 2006:S33) describe simple extraction methodology that allows removal of paracetamol and aspirin. The technique takes advantage of differential solubility of codeine phosphate (highly soluble) compared to paracetamol (poorly soluble) and aspirin (poorly soluble) (Cone, 2006:S31).

- A brief description of the method from Erowid's internet site, *Codeine FAQ*, as quoted by Cone (2006:S33) is as follows:

  > You can dissolve 20 tablets in 50 ml of hot water, cool the water down to 10°C, filter the solution and end up with the same amount of codeine as the tablets contained but only a fraction of the original amount of A/A.

  Although the above process appears to be effective in removal of paracetamol and aspirin, it does not remove caffeine and other water-soluble substances (Cone, 2006:S31).

- Acid–base extraction methods are detailed on the Internet on sites such as *The Opium Poppy FAQ*, as quoted by Cone (2006:S33), for purification of codeine from aspirin/caffeine preparations. The resulting codeine product from acid base extraction is the "free-base" form of codeine and purportedly can be administered by smoking.

- Another example of codeine tampering is found on the internet site *Sixthseal.com*, as quoted by Cone (2006:S33), which describes splitting a layered tablet containing codeine and ibuprofen (Nurofen Plus, available in Europe) into two portions, one-half purportedly containing codeine and the other half containing ibuprofen. The tablet is described as a large white elongated tablet with the logo "N+" on one side with the other side unmarked. A user commented that the tap of a pin on the tablet side would split the tablet down the center. One recreational user described splitting the tablet in half along the long axis and "taste testing" both sides. One side tasted "bitter" (presumably codeine) and the other side had a different flavour without bitterness. Another observer on the same site commented that Nurofen Plus tablets are now "unsplittable".

2.6.8 The involvement of analgesic abuse in the pathogenesis of analgesic nephropathy

Elseviers and De Broe (1996:S48) states that analgesic nephropathy is a chronic renal disease characterised by renal papillary necrosis and interstitial nephritis caused by excessive consumption of analgesic mixtures.

2.6.9 Dangers of chronic analgesic abuse

The chronic misuse of non-narcotic analgesics is connected with analgesic induced headache, gastrointestinal problems, analgesic nephropathy, and atherogenesis that may result in premature mortality (Meyers *et al.*, 2003:367).

According to Srikiatkhachorn (2000:343) chronic utilisation of analgesics can lead to a paradoxical deterioration of headache in patients with migraine and to a state known as analgesic-induced transformed headache.

2.7 Chapter summary

In this chapter the discussion centred on analgesics and the usage of combination analgesics as well as the aspects of pain and its management.

Pain is a very common complaint, and literature has revealed that combination analgesics are often used in it's treatment. According to Desmeules *et al.* (2003:8) the advantages of combining analgesics include increasing the duration of analgesia, widening the spectrum of efficacy, improved patient compliance and reduced parenteral abuse potential.

Specific focus was given to the abuse and associated dangers of analgesic drugs. The high prescribing rate and use of combination analgesics is a cause for concern, due to the dependence-producing potential of some of the ingredients.

Chapter 3
Healthcare – concepts and approaches.

3.1 Introduction

In this chapter the South African private health care system as well as the methods and techniques utilised by a pharmacy benefit management (PBM) company to obtain data for the assurance of quality health will be discussed. These include managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology.

3.2 The South African healthcare system

South Africa has a population in the region of 43 million. Even though South Africa is classified as a middle income country, approximately 35 to 55 percent of the population live in poverty and lack access to fundamental services including health care, clean water and sanitation (Ndimande, 2002).

According to Basset (2003), South Africa has a private and a public health care system with a grave discrepancy between the two, which reflects the country's first world/third world dichotomy:

- The public health care system, which is financed mainly by government subsidies and serves the mass of the population (Ndimande, 2002).
- The private health care system, which is administered by health insurance programs and only serves a small number of people who can pay for medical aid coverage/insurance (Ndimande, 2002).

3.2.1 The public health care system

According to Bletcher and Harrison (2006:32) the South African public health system provides nearly universal coverage i.e. all citizens are permitted to make use of it. Service points are extensively distributed and primary health care services are free at the point of service (Bletcher & Harrison, 2006:32).

According to Bletcher and Harrison (2006:32)

> health services are a basic constitutional right and right to use appears reasonably good with rising public health care utilisation and hospital utilisation rates fairly comparable with similar income countries.

However the quality of care is occasionally sub-optimal, because public facilities frequently have long waiting periods and primary care facilities tend to have few doctors and health professionals in service (Bletcher & Harrison, 2006:32).

According to Basset (2003), there are seven million South Africans with private health insurance, and an approximate 30% of those without insurance rarely consult doctors on a direct-paying basis. Nevertheless, 40% of the population lives in poverty and lacks that choice (Basset, 2003). About 80% of these people consult traditional healers, some of whom are trained by the Department of Health to provide primary healthcare (Basset, 2003).

According to Basset (2003) there are 6.9 million low-paid workers in the country with no medical insurance, and there is pressure to supply less sophisticated, low-cost schemes. But with health insurance contributions rising to an approximate 30% of people's incomes by 2007, it's likely that pressure on the public service will grow even more (Basset, 2003).

According to Ndimande (2002) South Africa has:

> well developed high technology hospitals in the main cities, but only the basic underdeveloped health care facilities and services in rural areas.

As a result, the poorer two thirds of the population do not have full access to primary health care services.

3.2.2 The private health care system

According to Ndimande (2005:6), South Africa has a large and highly developed private health care industry which plays an important role in the delivery of health care services.

According to Basset (2003), the private health care sector, loaded with sophisticated technology, serves just 16% of the populace who has private health insurance. There are more than two hundred private hospitals, owned by *consortia* of private physicians or large corporations (Basset, 2003).

According to Basset (2003) private health insurance fees are split 50/50 between employers and employees. Nevertheless, faced with medical inflation on one hand and legislation to implement 25%

solvency reserves on the other, medical insurance plans are struggling.

Managed healthcare prospers, as do inventive savings schemes (Basset, 2003). People can buy limited coverage or choose to pay for flu medication out of their own pockets and save their medical insurance payment for a big operation. Some medical schemes have cut costs by selecting lesser plans, leaving unsuspecting employees to face unforeseen bills, in which case they are often forced into the public sector (Basset, 2003).

According to Basset (2003) the standards of the South African private health care system are outstanding: the United Nations ranked South Africa's private system thirty ninth out of a hundred and sixty two nations for technological innovation and achievement. Worldwide, people fly to South Africa for operations, which are relatively cheap due of the country's weak currency (Basset, 2003).

3.2.2.1 Medical schemes

According to Dohority and McLeod (2002:44) there are two main categories of medical schemes.

- *Registered medical schemes* are those that rank completely under the regulatory control of the Medical Schemes Act (Act 131 of 1998); and
- *Bargaining Council schemes* which are those schemes that are not able to comply fully with the Act and are thus approved exemptions from certain of its requirements, mainly with respect to prescribed minimum benefits. Traditionally these schemes incorporated those covering the police service, correctional services and the defense force, as well as schemes that were created before the first Medical Schemes Act of 1967 (Dohority & McLeod, 2002:44).

According to the Council for medical schemes (2006) in 2005, a total of 6 835 621 beneficiaries were covered by medical schemes registered in terms of the Medical Schemes Act, 1998. This figure represents a 2.6% increase in covered lives from 2004 – compared to an overall estimated population growth rate for 2004- 2005 of 0.92%. During 2005, medical schemes covered 14.6% of the South African population (Council for medical schemes, 2006).

The lack of significant growth of the medical scheme population over the past decade, as shown in Figure 3.1, is indicative of the fact that medical schemes have been incapable to design packages that are

reasonably priced and attractive to the emerging market in South Africa (Bletcher & Harrison, 2006:54).

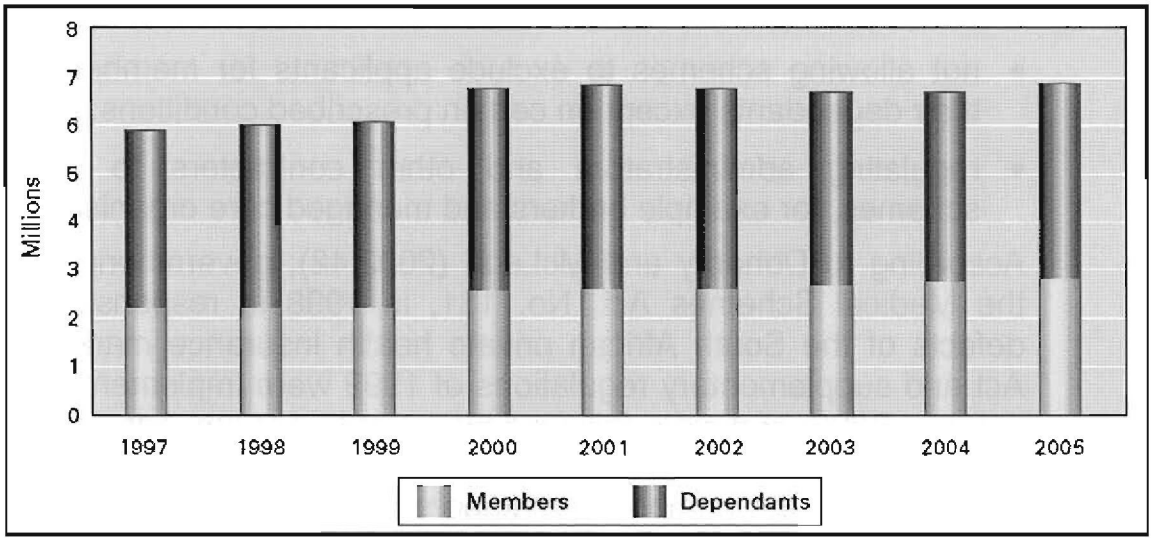

Figure 3.1 Beneficiaries of registered medical schemes (Bletcher & Harrison, 2006:54).

Major disparities remain in membership tariffs between provinces, closely related to the degree of differenciating employment levels between provinces. Expenditure patterns showed some noteworthy changes over the past year, including a considerable increase in the fraction of contribution income spent on health care benefits. Even though this is a positive development, it is not likely to be sustainable unless medical schemes manage to control increases in both health- and non-health expenditure better in the future (Bletcher & Harrison, 2006:62).

3.2.2.2 Medical schemes legislation

Private financing of health care in South Africa dates back to 1889 (Pearmain, 2000:2). The Medical Schemes Act was introduced in 1967. In 1993 major changes was implemented to the Act; many of a deregulatory nature. According to Pearmain (2000:2) the new Medical Schemes Act No. 131 of 1998 responded to these challenges by:

- introducing a Compulsory Minimum Benefits package for all schemes;
- prohibiting discrimination on the basis of age, medical history and health status;
- requiring that contributions be determined only on the basis of income and/or number of dependants;

- enabling schemes and public hospitals to have an agreement for the provision of minimum benefits to its members with payment for hospitals;
- not allowing schemes to exclude applicants for membership or their dependants except on certain prescribed conditions; and
- regulating administrators and other contractors to medical schemes, for example brokers and managed care organisations.

According to Dohority and McLeod (2002:42); government passed the Medical Schemes Act, No. 131, in 1998 in response to the defects of the South African private health insurance market. The Act and supplementary regulations of 1999 were implemented from January 2000, and were followed by a number of amendments. The primary objective of the Act is to force the extention of coverage in terms of both the number of members as well as the benefits they enjoy.

Furthermore, the Act made it obligatory for every scheme to accept all qualified applicants and to charge contributions that were differentiated only on the basis of income and the number of dependants, and not on age or the risk of ill-health (Dohority & McCleod, 2002:43). In addition, the Act made it obligatory for every scheme to cover an inclusive package of hospital and outpatient services, known as the Prescribed Minimum Benefits (PMBs) (Dohority & McCleod, 2002:43).

According to Dohority and McCleod (2002:43) the tool used by the Medical Schemes Act No. 131 of 1998 to reach its primary purpose was the combination of obligatory open enrolment, community-rating and Prescribed Minimum Benefits (PMB). Dohority and McCleod (2002:43) explained that:

> while community-rating and PMBs would increase the costs of cover for younger individuals, the designers of the Act hoped that the collective effects of opening up schemes to a large low-income market, creating larger risk pools and applying pressure to compete on the basis of efficiency, would bring down the costs of cover for the bulk of members.

3.2.3 Health care expenditure

South Africa's health care finance system is characterised by a public sector, financed through general tax revenue, and a private system dominated by medical schemes covering 15% of the population (Doherty *et al.*, 2002:14).

According to Doherty *et al.* (2002:14) South Africa will spend approximately R135 billion or 8% of Gross Domestic Product (GDP) in health sector financing mediators in 2006, an intermediary step in the financing path such as medical schemes and provincial Departments of Health, which lie between financing sources (e.g. households, employers) and expenditure areas (doctors, clinics).

Furthermore, R59 billion of the total amount will flow through public sector mediators (44%) and the remaining R75 billion through private financing mediators, of which about R59 billion will go through medical schemes (Doherty *et al.* 2002:14).

According to Basset (2003), the South African government annually spends the equivalent of approximately US$3.1 billion (at a late April 2002 exchange rate) on 35 million people, while the private sector spends US$36.5 billion on just seven million.

According to Ndimande (2002), a massive imbalance still exists in spending between the public and private health care sectors. Out of a total national health budget of about 70 billion Rands, only 10% of the total health care expenditure is in the public sector, which represents over 80% of the total population (Ndimande, 2002).

According to Ndimande (2002), market analysts predicted that the increase in health expenditure over the following three years would average 7,3% per annum, which is in balance with the other social services but, overall, less than the consolidated national expenditure which will increase by 8,% per annum over the next three years. This means that spending on health is falling behind (Ndimande, 2002).

Primary health care expenditure continues to grow strongly, reflecting the national emphasis on meeting basic needs and the centrality of primary health care in the national health system. Furthermore, growth in clinic and community health expenditure is particularly strong (Bletcher & Harrison, 2006:45).

3.2.4 Equity in health

In spite of the diverse definitions that exist, it appears that it has been agreed that the next core principles should be included in any definition of equity:

> The more needy groups in society should be the ones targeted for preferential treatment, that is, greater resources and more services should be made available to these groups (Ntuli, 2001:1).

Equity means the fair and sensible distribution of an reasonably priced package of quality health care services to the whole population of South Africa, irrespective of patients' ability to pay for such services and irrespective of their race, gender, sex, pregnancy, marital status, ethnic or social origin, colour, sexual orientation, age, disability, religion, conscience, belief, culture, language or birth; and 'equitable' has a corresponding meaning (DoH, 2005:8).

According to Ntuli (2001:1), South Africa reflects trends and patterns of inequity persisting all over the world in many ways: there are enormous differences between the rich and the poor per example a first world tertiary hospital stands side-by-side with clinics that lack basic infrastructure, electricity, running water and regular supply of drugs.

Ntuli (2001:1) states that the South African government is trying to encourage equity. To that end, the Constitution and policies of government commit the country to a national goal of "equity and equality".

The White Paper on Transformation of the Health System released by the Department of Health further expanded on this principle with the following equity-based core objectives;

- Increase in access to integrated health care services for all South Africans focusing on the rural, peri-urban and urban poor with emphasis on vulnerable groups (women and children) (Ntuli, 2001:1).
- Establish health care financing policies that promote greater equity between people living in rural and urban areas, and between people served by the public and private health care sectors (Ntuli, 2001:1).
- Distribute health personnel throughout the country in an equitable manner (Ntuli, 2001:1).

Within the South African health system, the current lack of health care personnel is most likely the most significant factor perpetuating inequity and needs to be addressed straight away. In this regard, the possibility of community participation and community health workers to reinforce services available to most disadvantaged communities must be factored into the equation (Khosa *et al*. 2004:36).

According to the DoH (2005:16-17) the general challenges with regard to equity in health services are:

- the lack of availability of a minimum defined basic package of health services to which everyone can have access irrespective of their capability to pay (DoH, 2005:16-17);
- discrepancies in the quality of health services across different groupings within the socio-economic spectrum (DoH, 2005:16-17);
- to eliminate stigmatisation of persons by the broader community, health personnel and health establishments on the basis of health conditions, reproductive decisions or treatment choices (DoH, 2005:16-17); and
- to eliminate unfair discrimination on the basis of sex, sexual orientation, gender, disability, health status, race, culture, religious beliefs and other prohibited grounds, from w within health establishments, the health professions, health services and the broader communities they serve (DoH, 2005:16-17);

Addressing inequities in our civilisation eventually depends on whether there is a political will, backed by the suitable resources to do so. Addressing inequities also depends on policy makers selecting political and strategic options which do not favour only economic growth in major provinces and cities, but also selecting a concerted pro-rural policy which focuses on improving life and support systems in these areas as a long term plan (Khosa *et al.*, 2004:36).

3.2.5 Public/Private partnerships (PPPs)

According to Morrison (2003:1), public-private partnerships involving governments, the private sector and civil society is gradually being recognised as:

> an international solution for social issues of almost every type – from building health care and clean water systems to sustaining the environment to bridging the digital divide.

The DoH (2005:10) states that public-private interactions (PPIs) include: public financing of health services provided by the private and/or non-government organisation sectors; private financing of publicly provided health services; innovative healthcare delivery models and business models for health practices; delivery models aimed at skill retention and effective distribution and utilisation of skills; use of public assets for the provision of health services by the private sector; use of private assets for the provision of health services by the public sector.

A good working definition for a public-private partnership includes three points. Firstly these partnerships engage at least one private for-profit organisation with at least one not-for-profit organisation. Secondly, the core partners provide a combined sharing of efforts and of benefits. Finally, partnerships in public health are committed to the formation of social value (improved health), espescially for disadvantaged populations (Reich, 2006:618).

According to Ndimande (2002) there are various reasons why public-private partnerships (PPP) are being explored in the South African health sector. One major reason is that the historical interaction between the public and private sectors has not been positive, and has resulted in a strong negative net effect on the public sector.

Therefore a fairly substantial subsidy from the public to the private sector has become visible. An insufficient regulatory environment has helped to aggravate the situation. PPPs are therefore seen as one way to tap into the concentration of resources to the benefit of all citizens (Ndimande, 2002).

Until recently, the government treated the public and private sectors as two distinct entities that could be managed separately. Experience has shown that, if left unregulated, the private sector will infringe on public objectives. Therefore it has led to an understanding that government needs to influence the behaviour of the private sector through regulation, hence the enactment of the Medical Schemes Act of 1998. It is also documented that government needs to seek out opportunities for productive partnerships with the private sector in order to tap into the huge resources at its disposal (Ndimande, 2002).

One form of public-private relationship is public financing of private sector care for public patients and the second form of public-private relationship is private financing of public care. Thirdly, there is another form of association that occurs between the public and private sectors, namely, public financing of care (public or private) for private/insured patients (Ndimande, 2002).

Figure 3.2 attempts to provide an extended structure to consider the intricacy of the relationships that may exist between the public and private sectors.(Wadee *et al.*, 2004:14).

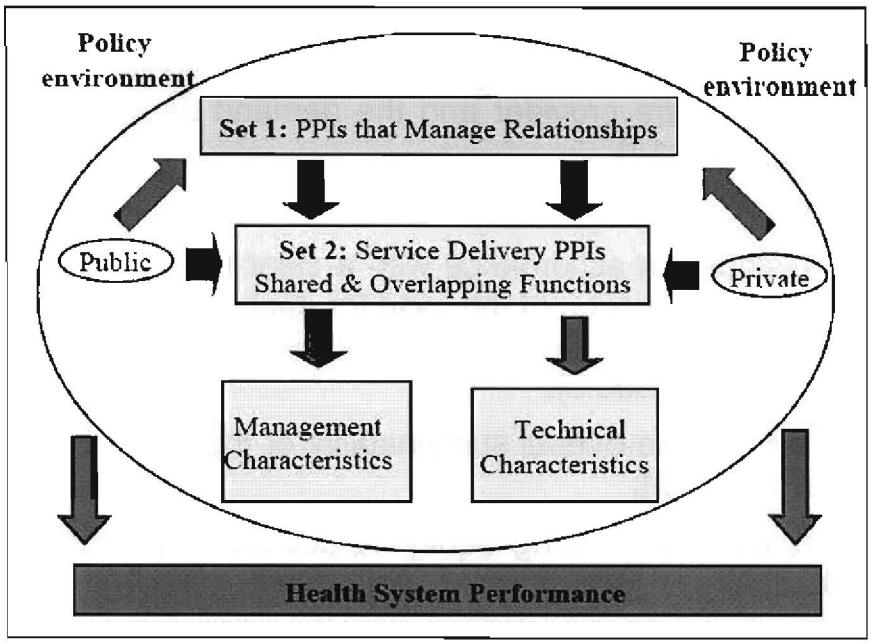

Figure 3.2 Functions of private and public sectors in relation to health sector service delivery (Wadee *et al.* 2004:14).

It is functional to provide a summary of each of the components of Figure 3.2 (Wadee *et al.* 2004:14).

- The *policy environment* considers: the context in which PPIs are taking place; the key stakeholders, the role they play and what their objectives might be in relation to each other; the evolution of PPI development internationally and nationally as well as the processes that allow for PPI policy development (Wadee *et al.*, 2004:14).
- There are two different sets of PPIs that have been identified and highlighted within the framework – *PPIs that manage relationships* and *service delivery PPIs* (Wadee *et al.*, 2004:14).
- *PPIs that manage relationships* consider both the formal and informal dialogue that exists in facilitating the development and implementation of PPIs (Wadee *et al.*, 2004:14).
- *Service delivery PPIs* allow one to capture the overlapping of functions with respect to both financing and provision, whilst unpacking the complex nature of shared functions. This is achieved by distinguishing between the *management* and the *technical characteristics* of PPIs (Wadee *et al.* 2004:14).
- The *management characteristics* consider the level of management, the service of focus and the private sector agent (Wadee *et al.*, 2004:14).

- The *technical characteristics* assist in identifying respective functions with respect to capital/recurrent financing, capital ownership, healthcare provider and the demand decision-maker (Wadee *et al.*, 2004:14).

The Department of Health (2005:5) requires that PPIs:

- must be developed in accordance with a clear frame that allows for a thorough investigation of the case for each PPI, a sound and cost effective implementation and sufficient public reporting mechanisms (DoH, 2005:5);
- must contribute to the overall sustainability of the national health system (DoH, 2005:5);
- must contribute to promoting equity of access to primary care (DoH, 2005:5);
- must contribute to promoting equity of access to affordable health care and strengthened public hospital care (DoH, 2005:5); and
- must contribute to promoting equity in financing of health services (DoH, 2005:5);

3.2.6 Challenges for the South African health care system

According to Basset (2003), the South African health care system currently faces many challenges. The most serious challenges for health care personnel include: low salaries; despair about AIDS and the government's unwillingness to provide clear treatment guidelines and lack of basic infrastructure such as roads and telephones in distant rural areas, which makes tuberculosis (TB) testing difficult.

The most important challenge facing the South African health system is to tackle the unproductive and unfair distribution of resources between the public and private health care sectors relative to the population served by each sector (DoH, 2005:18).

Access to health care is a multifaceted issue of legitimate significance. There are significant numbers of people in South Africa who do not have sufficient access to health services due to geographical, financial, physical, communication, sociological (such as unfair discrimination and stigmatisation) and other barriers. Better "access" requires better efficiency, since increases in efficiency should lead to increased access (DoH, 2005:13).

Incompetence in the national health system threatens its sustainability since it leads to maldistribution of resources, and undermines policies and procedures intended to give effect to the distribution, allocation or utilisation of resources (DoH, 2005:14).

According to Basset (2003) the biggest challenge facing the South African health care sector is still HIV-AIDS. There are 2.4 million HIV-infected people in South Africa. Already Johannesburg hospitals areb admitting 100 full-blown HIV-cases daily.

3.2.7 Drug pricing structure

The National Drug Poilcy's aim to promote the availability of safe and effective drugs at the lowest possible cost will be achieved by monitoring and negotiating drug prices and by rationalising the drug pricing system in the public and private sectors, as well as promoting the use of generic drugs (DoH, 1996:9).

Drug prices in South Africa are monitored and regulated by a Pricing Committee within the Ministry of Health. Committee members include health economists, pharmacoeconomists, representatives from the Department of Finance, the Department of Trade and Industry, the Procurement Unit of the Department of Health, the Department of State Expenditure, and consumer representatives (DoH, 1996:9).

The medicine regulations implemented in 2004 stated that only a dispensing fee of 26% for the medicine with a single exit price (manufacturer's price) of R100 and below should be charged. Where the single exit price is higher than R100, a maximum of R26 dispensing fee can be charged (Tshabalala-Msimang, 2005).

The introduction of the medicine pricing regulations in 2004 led to a court challenge by retail pharmacies. The matter was heard in the Cape High Court, Supreme Court of Appeal and ended in the Constitutional Court judgement of 30 September 2005 which declared that the dispensing fee regulations were invalid. The court recommended that the Pricing Committee reconsider the fee of 26% of the single exit price capped at R26, giving due regard to the viability of retail pharmacies (especially rural and courier pharmacies) (Tshabalala-Msimang, 2006).

On 31 October 2006, a new dispensing fee was announced. According to Tshabalala-Msimang (2006) the new dispensing fee should be calculated as follows:

- where the single exit price of a medicine is less than seventy five rands, the dispensing fee, is a total of four rands plus 33% of the single exit price of the medicine (Tshabalala-Msimang, 2006);
- where the single exit price of a medicine is seventy five rands or more but less than two hundred and fifty rands, the dispensing

fee is a total of twenty five rands plus 6% of the single exit price of the medicine (Tshabalala-Msimang, 2006);

- where the single exit price of medicine is two hundred and fifty rands or more but less than one thousand rands, the dispensing fee is a total of thirty three rands plus 3% of the single exit price of the medicine (Tshabalala-Msimang, 2006); or
- where the single exit price of a medicine is one thousand rands or more, the dispensing fee is a total of fifty rands plus 1.5% of the single exit price of the medicine (Tshabalala-Msimang, 2006).

It is anticipated that the price of medicines will be further reduced after the implementation of international benchmarking. This may reduce the dispensing fee income so the committee has decided to review the dispensing fee after the implementation of the benchmarking methodology (Tshabalala-Msimang, 2006).

3.2.8 The use of generic drugs

The use of interchangeable multi-source pharmaceutical products, using the international nonproprietary name (INN), or generic name, is a recommended step to reduce drug costs and expenditure. It also contributes to a sound system of procurement and distribution, drug information and rational use at every level of the health care system (DoH, 1996:10).

In 2003, the Medicines and Related Substances Control Amendment Act (Act 90 of 1997), made it compulsory for pharmacists to offer customers a generic substitute, regardless of what the prescriber has written. This is assuming that the drug is off-patent and a generic is available (Deeney, 2003:453).

3.3 Managed health care

3.3.1 Concept and definition

Anon (2006b) described managed health care as

> systems and techniques used to control the use of health care services.

It includes a review of medical requirements, incentives to use certain providers, and case management. In addition, managed health care is *"the body of clinical, financial and organisational activities"* designed to guarantee the provision of suitable health care services in a cost-efficient manner (Anon, 2006b).

Managed care has a number of plans which offers a range of features that vary in their abilities to balance access to care, cost, quality control, benefit design and flexibility (Wagner, 1997:48).

Managed care is a broad term and encompasses many diverse types of organisations, payment mechanisms, review mechanisms and collaborations. Managed care is sometimes used as a universal term for the activity of organising doctors, hospitals, and other providers into groups in order to improve the quality and cost-effectiveness of health care (Anon, 2006b).

According to Lyles and Palumbo (1999:136) managed health care is a cost-effective way to comply with the needs as related to pharmaceutical services. There are many techniques available to influence the purchasing and prescribing practices, but the availability and systematic use of studies which can link these practices to clinical and economic outcomes are limited.

Managed health care is a system of health care delivery which influences the utilisation of services, and therefore it measures performance (Valiotes *et al.*, 1993:37).

According to Anon (2006b) the term managed care is often misunderstood, as it refers to numerous aspects of healthcare management, payment and organisation. People working in healthcare and medical insurance can be viewed as "managing care." As a result, managed care is any system of health payment or delivery arrangements where the plan attempts to control or organise use of health services by its enrolled members in order to contain health expenditures, improve quality, or both (Anon, 2006b).

3.3.2 Objectives of managed health care

According to Gouws (1996:246) the primary objective of managed health care is the containment of health care costs and promoting the provision of quality health care services at affordable levels.

3.3.3 Basic principles of managed health care

Managed care techniques are most often practiced by organisations and professionals that assume risk for a defined population (e.g., health maintenance organisations) but this is not always the case (Anon, 2006b).

According to Gouws (1996:246) managed health care and the control of costs might further stimulate the implementation of drug formularies and inadequate drug lists, increase the use of generic products, increase the number of Health Monitoring Organisations

(HMO's) and might force medical aids to put extra limits on member benefits.

3.3.4 Managed health care plans

According to Anon (2006b) a managed care organisation is a body that manages risk, contracts with providers, is paid by employers or patient groups, or handles claims processing.

According to the American heart association (2006) there are three major types of managed care plans, which each has systems with distinguishing features or characteristics.

3.3.4.1 Health Maintenance Organisations (HMO)

According to Edwards (1998:3) a Health Maintenance Organisation (HMO) is a health care system that provides comprehensive health services to enrolled persons living within a specific geographic region and which could be responsible for both delivering and financing health services.

A Health Maintenance Organisation (HMO) is a prepaid medical service in which members pay a monthly or yearly fee for all health care, including hospitalisation (Anon, 2004).

An HMO enters into contractual activities with healthcare providers (e.g., doctors, hospitals and other healthcare professionals) who together form a "provider network" (American heart association, 2006).

Because costs to patients are fixed in advance, preventive medicine is stressed, to avoid costly hospitalisation.

> A contracted provider is one who provides services to health plan members at discounted rates in exchange for receiving health plan referrals (American heart association, 2006).

One criticism of HMO's is that patients can use only doctors and specialists who are associated with the organisation. *Open-ended* HMO's offer members the option of seeing a doctor who is not part of the HMO, but the patient must pay additional costs (Anon, 2004).

Proponents of HMO's states that they make health care available to more people and that their emphasis on prevention results in earlier diagnosis and increased health-care savings (Anon, 2004).

3.3.4.2 Preferred Provider Organisations (PPO)

According to the American Heart Association (2006) PPO's are similar to HMO's in that they enter into contractual activities with healthcare providers who together form a "provider network." PPOs

are less restrictive than HMOs in the choice of health care provider. However, they tend to require greater *out-of-pocket* payments from the members (American Heart Association, 2006).

3.3.4.3 Point-Of-Service Plans (POS)

According to the American Heart association (2006) a point-of-services plan (POS) is often called an HMO/PPO hybrid or an "open-ended" HMO. The reason it's called "point-of-service" is that members choose which option – HMO or PPO – they will use each time they seek health care. POS plans are becoming more accepted because they offer more elasticity and freedom of choice than standard HMOs (American Heart association, 2006).

A point-of-service plan (POS) is a type of managed care plan that is a hybrid of HMO and PPO plans. Like an HMO, participants designate an in-network physician to be their primary care provider. But like a PPO, patients may go outside of the provider network for health care services. When patients venture out of the network, they will have to pay most of the cost, unless the primary care provider has made a referral to the out-of-network provider. Then the medical plan will settle the ammount (CHF, 2007).

3.4 Drug utilisation review (DUR)

3.4.1 Introduction to Drug Utilisation studies

In 1995 Truter *et al.* (1995:19) identified that drug utilisation research was a comparatively unexplored field in South Africa in spite of its significance in economic planning, in improving prescribing habits and in promoting the most favourable use of limited resources. They concluded that drug utilisation research can play a vital role in the promotion of rational and cost-effective use of medicine in South Africa (Truter *et al.*, 1995:19).

According to Sena and Pashko (1993:900) drug utilisation review (DUR) provides a method for studying drug use through the review of medical and pharmaceutical records, with the goal of quantifying the medical and cost-effectiveness of drug therapy.

3.4.2 Defining Drug Utilisation Review (DUR)

The World Health Organization (2003:8) defined 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.

According to Truter (1997:19) this extensive definition focuses primarily on the drug use process, including the economic consequences. The definition includes the terms "society", as well as an economic term, consequently the method has an obvious emphasis on socio-economic factors (Truter, 1997:19).

Serradell et al. (1987:994) defined drug utilisation as

> the prescribing, dispensing, administering, and ingesting of drugs.

According to Stolar (1978) a DUR programme is an ongoing method of assuring the quality of drug use through the employment of standards and efforts to correct drug use not consistent with these standards; the effectiveness of corrective actions is measured.

3.4.3 Overview of DUR

Edgren (1996:117) described DUR as authorised, structured and continuing procedures that review, analyse, and interpret patterns of drug use.

DUR aims to control an assure quality to enhance the use of pharmaceuticals. Quality control includes appropriateness of dose or duration of therapy, while quality assurance relates to measuring outcomes of therapy with drugs (Erwin, 1991:596).

According to the World Health Organization (2003:8) drug utilisation review can be divided into descriptive and analytical studies. The emphasis of descriptive studies has been to explain patterns of drug utilisation and to identify problems worthy of more detailed studies. Analytical studies try to connect drug utilisation data to figures on morbidity, outcome of treatment and quality of care with the final goal of assessing whether drug therapy is rational or not (WHO, 2003:8).

According to Sjöqvist and Birkett (2003:77) DUR provides the mechanism for developing standards, assessment of current therapies, the implementation of specific interventions and the reassessment of drug utilisation.

According to Sjöqvist and Birkett (2003:77) drug utilisation research is an essential part of pharmaco-epidemiology as it describes the extent, nature and determinants of drug exposure. In common use, the distinction between these two terms has become less sharp, and they are sometimes used interchangeably.

According to the World Health Organization (2003:8-9), drug utilisation research and pharmaco-epidemiology may supply insights into the following aspects of drug use and drug prescribing:

- Pattern of use: The degree and profiles of drug use and the trends in drug use and costs over time (WHO, 2003:8).
- Quality of use: Indications of quality of drug use may contain the choice of drug, drug cost, drug dosage, alertness of drug interactions and adverse drug reactions, and the amount of patients who are aware of or unaware of the costs and benefits of the treatment (WHO, 2003:8) .
- Determinants of use: User characteristics (e.g. socio-demographic parameters and attitudes towards drugs), prescriber characteristics (e.g. speciality, education and factors influencing therapeutic decisions) and drug characteristics (e.g. therapeutic properties and affordability) (WHO, 2003:9).
- Outcomes of use: Health outcomes (i.e. the benefits and adverse effects) and the economic consequences WHO, 2003:9).

According to Blackburn (1993:14) the goal of DUR is:

> to improve the quality of patient care through the prescription and use of appropriate drugs in conditions for which use, based on sound medical judgement, is indicated and at a minimal cost consistent with an acceptable quality of care (Blackburn, 1993:14).

3.4.4 Classification of Drug Utilisation Review

According to Stolar (1978:76) DUR studies can be classified as quantitative or qualitative.

3.4.4.1 Quantitative DUR

Quantitative studies involve the collection, organisation and display of estimates or measurements of amounts of drug use (Stolar, 1978). Quantitative DUR studies may be episodic or continuing activities, and are typical functions of the pharmacist or pharmacy department (Kreling & Mott, 1993:416).

The object of quantitave studies is to quantify the present state, the developmental trends, and the time course of drug usage at various levels of the health care system, whether national, regional, local or institutional (Lee and Bergman, 1994:379).

According to Sacristan and Soto (1994:300) quantitative DUR can be used to:

- analyse the amount of drugs consumed in a specific geographical area;

- compare the consumption/prescribing patterns of drugs in different geographical areas;
- identify areas of over- and under-prescribing;
- look into the utilisation of drugs according to demographical features;
- estimate misuse of drugs; and
- observe the impact of informational or regulatory activities on drug use patterns.

According to Stolar (1978:76) data from quantitative DUR studies should in general be considered suggestive, not conclusive, with respect to quality of drug use.

3.4.4.2 Qualitative DUR

Qualitative studies on the other hand, assess the appropriateness of drug utilisation, usually by linking prescription data to the reasons for the drug prescribing (Lee and Bergman, 1994:379).

According to Stolar (1978:76) qualitative studies are multidisciplinary operations which collect, organise, analyse and report information on the rationality of the drug use base.

According to Kreling and Mott (1993:416) and Sacristan and Soto (1994:300) qualitative DUR can be used to:

- assess the suitability of the daily dosage;
- analyse the period of time of therapy;
- establish the indication of use of the specific drug or non-drug regimen;
- recognise potential drug interactions;
- establish the most suitable dosage for each indication; and
- assess the fixed combination of drugs.

3.4.5 Classification of drug utilisation studies

3.4.5.1 Prospective DUR

According to Kreling and Mott (1993:417), prospective DUR's offers a direct benefit to the patient, because it identifies and prevents drug therapy problems before they occur.

The prospective DUR process is best built on trends identified in previous retrospective DUR, but may also be based on compendia,

published literature, clinical experience, and basic pharmacologyprinciples (Erwin, 1991:596).

This type of DUR has the greatest potential benefit for the patient, because it identifies drug therapy problems and corrects them before they can occur (Kreling & Mott, 1993:417).

3.4.5.2 Retrospective DUR

According to Hennessy *et al.* (2003:1494) a retrospective drug utilisation review programme is a structured ongoing plan that interprets patterns of drug use in relation to predetermined criteria and attempt to minimise inappropriate prescribing. This type of review takes place after the prescription has been dispensed (Hennessy *et al.*, 2003:1494).

According to Serfontein and Hendriks (2000:8) retrospective DUR has a number of advantages:

- it can be performed rather effortlessly using a data base from a medical aid;
- information and drug therapy trends in certain geographical areas can be analysed and if required it can be changed by using the suitable interventions;
- inappropriate prescribing practices can be identified and through educational interventions with the doctor these problems can be eradicated. This will lead to rational prescribing and better quality treatment for the patients; and
- it is a relatively inexpensive type of DUR method with a variety of interesting applications.

Even though retrospective DUR studies have little impact on immediate patient care, it serves to identify trends in prescribing practices that may lead to interventions aimed at enhancing prescribing behaviour (Truter, 1995:20).

3.4.5.3 Concurrent DUR

Concurrent review is generally undertaken before the pharmacist dispenses the drug to the patient and it focuses on the appropriateness and correctness of the drug prescribed (Blackburn, 1993:15).

According to Blackburn (1993:15) this type of review is very limited, therefore it is only used for selected institutionalised or chronic patients. A concurrent review is more expensive and time consuming than retrospective studies, but has the potential for much

greater results in the prevention of problems (Wertheimer, 1988:155).

3.4.5.4 Types of DUR studies

- Cross-sectional studies

The World Health Organization (2003:17) describes cross-sectional data as *"data, which provide a 'snapshot' of drug use at a particular time (e.g. over a year, a month or a day)"*. The studies can be used to make comparisons with similar data collected over the same period in another health facility, ward or country, and could be drug-, problem-, indication, prescriber- or patient-based.

Alternatively, a cross-sectional study can be carried out before and after an educational or other intervention. Studies can merely measure drug use, or can be criterion-based to assess drug use in relation to guidelines or limitations (WHO, 2003:17).

- Longitudinal studies

Longitudinal data is necessary for public health authorities to study trends in drug use. Drug-based longitudinal data can be on total drug use as obtained through a claims database, or the data may be based on a statistically valid sample of pharmacies or medical practices (WHO, 2003:17).

Longitudinal data is often obtained from frequent cross-sectional surveys. Data collection is a constant process, but the practitioners and patients surveyed, are constantly changing. Such data gives information about overall trends, but not about prescribing trends for individual practitioners or practices (WHO, 2003:17).

- Continuous longitudinal studies

According to the WHO (2003:170) continuous longitudinal data can in some cases be obtained at the individual practitioner and patient level. Claims databases are often able to follow individual patients using a unique identifier. This data can then provide information about concordance with treatment based on the period amid prescriptions, co-prescribing, duration of treatment and Prescribed Daily Doses (PDD's) (WHO, 2003:17).

3.4.6 Uses of DUR studies.

3.4.6.1 Description of drug use patterns

Drug utilisation research can improve our understanding of how drugs are being used as follows:

- it can be used to approximate the numbers of patients exposed to specific drugs within a given time period. Such estimates may either refer to all drug users, despite the commencement of drug usage (prevalence), or focus on patients who started to use the drug within the select period (incidence) (Sjöqvist & Birkett, 2006:78);
- it can explain the extent of use at a certain moment and/or in a specific area (e.g. in a country, region, community or hospital). Such descriptions are most significant when they form part of a constant evaluation system, i.e. when the patterns are followed over time and trends in drug use can be discerned (WHO, 2003:9);
- researchers can approximate to what extent drugs are correctly used, overused or underused (Sjöqvist & Birkett, 2006:78);
- it can establish the pattern or profile of drug use and the degree to which alternative drugs are being used to treat particular conditions (WHO, 2003:9);
- it can be used to compare the experimental patterns of drug use for the treatment of a specific disease with present recommendations or guidelines (WHO, 2003:9);
- it can be used in the application of quality indicators to patterns of drug utilisation. This universal indicator can be applied at diverse levels (e.g. individual prescriber, group of prescribers, hospitals, region or county) to obtain a rough approximation of the quality of prescribing (Sjöqvist & Birkett, 2006:79);
- drug utilisation data can be processed and feedback can be given to prescribers (WHO, 2003:9); and
- the number of case reports about a drug problem or side effects can be related to the amount of patients exposed to the drug to assess the potential magnitude of the problem. If it is probable to detect that the reaction is more common in a certain age group, in certain conditions or at a given dose level, improving the information on indications, contraindications and suitable dosages may be sufficient to ensure safer use and avoid withdrawal of the drug from the market (Sjöqvist & Birkett, 2006:79).

3.4.6.2 Interventions to improve drug-use follow up

Drug utilisation review undertaken in the following ways may allow us to assess if interventions projected to improve drug use have had the preferred impact.

- The result of actions taken to eradicate undesirable drug-use patterns (e.g. information campaigns, provision of formularies, and regulatory policies) has to be monitored and evaluated (WHO, 2003:10).
- The impact of changes in insurance or reimbursement systems or regulatory changes should be assessed using a broad survey. This is essential because the total cost to society may stay the same or may even increase if more expensive drugs are used as alternatives (Sjöqvist & Birkett, 2006:79).
- The degree to which the educational activities of the society and the promotional activities of the pharmaceutical industry affect the patterns of drug use should be assessed (Sjöqvist & Birkett, 2006:79).

3.4.6.3 Quality control of drug use

Drug use should be controlled according to a quality control cycle (Fig 3.3) that offers a methodical framework for constant quality improvement (WHO, 2003:10).

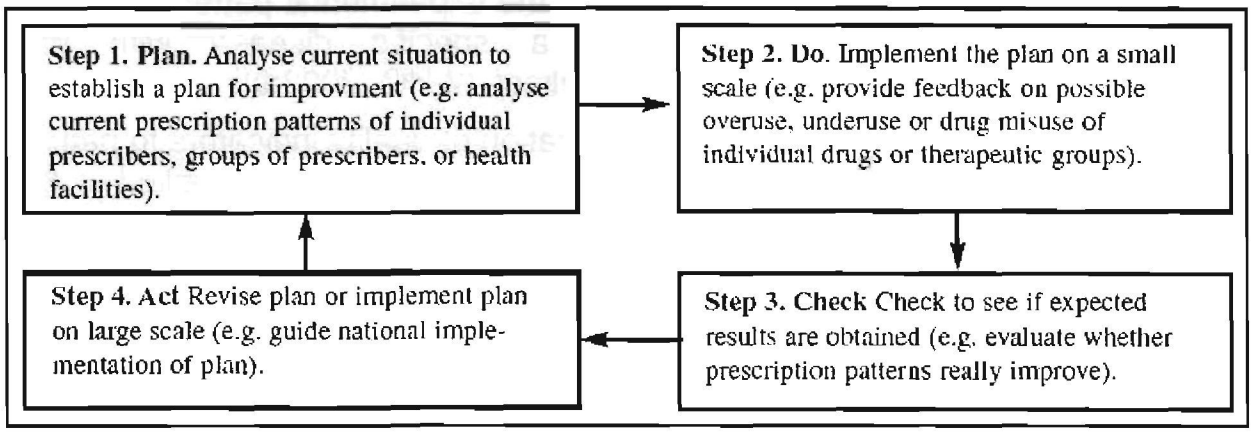

Figure 3.3: The quality control cycle (WHO, 2003:11).

According to the WHO (2003:10) the quality control cycle can be functional at many levels, from local or regional discussion groups consisting of physicians, clinical pharmacologists or pharmacists to national and international initiatives. A vital technique that can be used in combination with this cycle is benchmarking. By comparing drug utilisation data from diverse localities, it is frequently possible to detect substantial differences that require further evaluation, which may then lead to the recognition and promotion of best practice. Such comparisons will be accurate and truthful provided that the

data are collected and aggregated in a standardised, uniform way (WHO, 2003:11).

3.4.7 Objectives of DUR studies

According to the WHO (2003:9) the principal aim of drug utilisation research is to facilitate the rational use of drugs in populations. For the individual patient, the rational use of a drug implies the prescription of a well-documented drug at an optimal dose, together with the correct information, at an affordable price.

3.4.8 Drug utilisation studies that can be used in pharmacoeconomic studies

The different drug utilisation studies which can be used in pharmacoeconomic studies are summarised in Table 3.1.

Table 3.1 Drug utilisation studies that can be used in pharmacoeconomic studies (Adapted from Truter 1997:15-20).

• **Identification of research areas**
Areas of health care with the potential to reduce expenses and advance the quality of patient care is often disregarded because of the lack of data, or because data is not in a standardised format that permits comparison. One of the pre-requisites for dur-studies is a dependable and comprehensive database.
• **Morbidity data**
Many underdeveloped countries, have no statistics on disease incidence at their disposal. Dur-studies can serve to approximate the prevalence of an illness in a specific area, based on consumption data for the drug(s) used to treat the disease. Dur-studies can also be used to evaluate prevalence of an illness in different areas, or to examine different prescribing practices.
• **Cost of drugs**
The cost by day of treatment is an accepted unit of measurement in drug utilisation studies. The treatment cost per day, plus the remaining costs (direct and indirect), can be used in any type of pharmacoeconomic study, particularly in cost-minimisation studies. Comparisons of the total cost of a drug or therapeutic class of drugs between geographical areas can also be carried out.
• **Cost of treating an illness**
Drug utilisation studies allow the estimated calculation of the cost of the drugs used to treat a particular illness. This together with other direct and indirect costs, can be used to calculate the total cost of treating an illness.
• **Detection/correction of problems**
Drug utilisation studies can recognise differences in drug usage, particularly aspects such as the overuse, misuse, under-use and incorrect use of drugs, as well as non-compliance. The information can be used to measure the economic significance of the inappropriate use of drugs.
• **Studies of therapeutic compliance**
Compliance studies can be used to get hold of information about the effectiveness of a drug. This data can give information to determine the real-world effectiveness of drugss.
• **Adverse drug reactions**
Drug utilisation studies can be used to estimate the incidence of side effects, which in turn can be used to calculate the treatment cost of adverse drug reactionss.
• **Effectiveness of drug therapy**
Drug utilisation studies can be used to assess the overall quality of drug therapy, as well as examining prescribing quality. This information can be used in pharmacoeconomic studiess.
• **Choice of comparator drugs**
Drugs can be recognised which are commonly used for a specific indication,

and this information can then be used to choose drugs with comparable or equivalent outcomes in pharmacoeconomic studies.
• **Identification of priorities**
Information about drug groups that have the maximum consumption, the therapeutic value of these drugs and areas for improvement in prescribing can help those interested in the development of new drugs, to make the most of the benefit of resources that are invested to research.
• **Monitoring of interventions**
The purpose of drug utilisation studies is not only the detection of problems, but also establishment of measures or interventions to solve them.
• **Improved prescribing practices**
Drug utilisation, through interventions, can improve prescribing practices and drug usage. Such improvements should be reflected by an increase in the efficiency and safety of drugs and are often coupled with lower total costs.

3.4.9 Defining the unit of measurement

- Defined daily dose

The World Health Organization (2003:38) defines the Defined Daily Dose (DDD) as:

> the assumed average maintenance dose per day for a drug used for its main indication in adults.

According to Lee and Bergmann (1994:16) the defined daily dose methodology was developed in response to the need to convert and standardise readily available volume data from sales statistics of pharmacy inventory data, into medically meaningful units, to make rough estimates of the number of people exposed to a specific drug or class of drugs.

The defined daily dose is a unit of measurement and does not necessarily agree with the recommended or prescribed daily dose (PDD). Doses for individual patients and patient groups will often differ from the DDD and have to be based on individual characteristics (e.g. age and weight) as well as pharmacokinetic and pharmacogenetic considerations (Sjöqvist & Birkett, 2006:83).

- Prescribed daily dose

The prescribed daily dose (PDD) was defined by the WHO (2003:39) as *"the average dose prescribed according to a representative sample of prescriptions."* The PDD can be established from studies of prescriptions or medical- or pharmacy records. It should be noted that the prescribed daily dose does not necessarily reflect actual drug utilisation. Some prescribed

medications are not dispensed, and the patient does not always take all the medications that are dispensed (Sjöqvist & Birkett, 2006:84).

- Cost

Drug use can be expressed in terms of costs. Cost figures are appropriate for an in general analysis of expenditure on drugs (WHO, 2003:39).

According to the WHO (2003:40) international comparisons based on cost parameters can be deceptive and have restricted value in the evaluation of drug use. Price differences between alternative preparations and different national cost levels make the assessment difficult. Long-term studies are also complicated due to fluctuations in currency and changes in prices (Sjöqvist & Birkett, 2006:83).

When cost data are used, an increase in the use of cheaper drugs may have little influence on the total level of spending on drugs, while a change to more expensive drugs is more willingly noticed. (WHO, 2003:40).

- Numbers of prescriptions

Numbers of prescriptions do not precisely reflect total use, unless total quantities of drugs per prescription are also taken into account. However, counting of prescriptions is valuable in measuring the frequency of prescriptions and in evaluating the clinical use of drugs (e.g. diagnosis and dosages used) (WHO, 2003:39).

3.4.10 The potential contribution of DUR studies to health care in South Africa

One of the aims of the South African National Drug Policy is to promote the rational prescribing, dispensing and use of drugs by medical, paramedical and pharmaceutical personnel and to support the informed and appropriate use of drugs by the community. To ensure rational prescribing the Department of Health will collect, evaluate and disseminate systematic data on drug utilisation to monitor and act on policy adherence (DoH, 1996:18).

3.5 Pharmacoeconomics

3.5.1 Defining pharmacoeconomics

Pharmacoeconomics has been formally defined by Bootman *et al.* (1996:4) as "*the description and analyses of the costs of drug therapy to healthcare systems and society.*" According to Truter (1997:19) pharmacoeconomics is a developing discipline that is committed to the study of how different approaches to patient care

and treatment influence the resources consumed in healthcare. Gouws (1996:246) describes pharmacoeconomic research as identifying, measuring and comparing the costs and consequences of pharmaceutical products and services.

Truter (1997:19) points out that the definition for pharmacoeconomics includes the terms "society", as well as an economic term, therefore the method has a clear emphasis on socio-economic factors. According to Cantor (2002:S29) it is an interdisciplinary science that incorporates elements from pharmacy, clinical medicine, clinical epidemiology, statistics, psychology, economics, and ethics.

3.5.2 Objectives and importance of pharmacoeconomic studies

According to Li (2003:192) healthcare providers worldwide are faced with the challenge of adapting to recent and anticipated future reforms in healthcare policy aiming to control the ever-increasing healthcare costs. Thus, to maintain a correct balance between the trio health care goals of adequate access, high quality and acceptable cost in healthcare delivery, is becoming more difficult. This is especially the case for the clinician as he or she is forced to make the decision about using newer and more expensive drugs and technologies when drug budgets are shrinking. As a discipline, pharmacoeconomics promises to assist in providing the answer (Li, 2003:193).

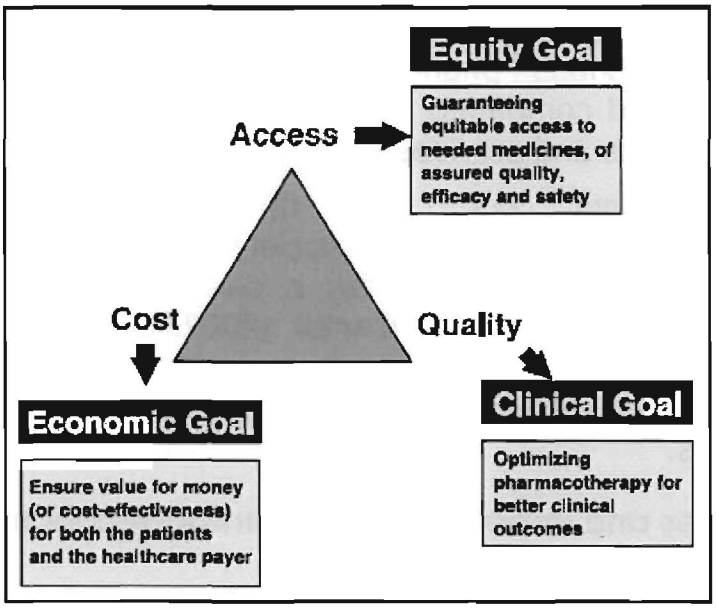

Figure 3.4 Goals of health care (Li, 2003:193).

Pharmacoeconomics has been described by Orešković (2002:27) as a modern scientific branch of medicine whose importance in drug development and marketing began to be recognised in the 1990-ties.

To date the objective of pharmacoeconomics has been to generate information that will influence customer groups, gain regulatory and reimbursement approval and lead to enhanced commercial success. A further key objective of engaging in pharmacoeconomics, the business of drug development, is still underdeveloped. Drug development involves many resources and many choices (Miller, 2005:2).

The ultimate aim of pharmacoeconomics is to assist the decision makers in achieving allocation efficiency in the healthcare system (Li, 2003:192). According to Gouws (1996:246) this is accomplished by pharmacoeconomical research consisting out of the analytical approach to identify, measure and compare the consumption of resources and to analyse and describe the consequences of consumption.

Health insurance societies, ministries of health, medical schools, schools for public health and the pharmaceutical industry are all aware of the importance of specialising and gaining knowledge in this particular field. The rising costs of medical care lead the manufacturers and buyers of medical instruments and pharmaceutical products to recognise the need to evaluate and compare the cost of investments and expenditures regarding the effects achieved. This surpasses the traditional criteria of efficiency

and safety valid before the advent of pharmacoeconomics in investigation, registration, financing, prescribing and utilisation of drugs (Orešković, 2002:28).

According to the WHO (2000:8) economic evaluation is one of the tools available to help choose wisely from a range of alternatives and implement efficient resources.

Miller (2005:11) specified that no amount of pharmacoeconomic data can make a bad drug good; what it can do is enhance the drug developers understanding of the characteristics of that drug. Decision-making in light of this information is likely to be better than that without it, whether it leads to faster termination of uneconomic projects or the allocation of more appropriate resources to attractive projects.

3.5.3 Conducting pharmacoeconomic analyses

According to Miller (2005:3) pharmacoeconomic analysis early in the drug development process can provide valuable input into:

- the design of clinical and non-clinical development programmes;
- project selection and termination decisions; and
- the optimal pricing strategy.

Hence, early pharmacoeconomic evaluations may help with a number of key decisions such as the selection of candidate drugs to develop, choice of indication, clinical study designs and pricing strategy (Miller, 2005:3).

Li (2003:193) defines pharmacoeconomic evaluations as the comparison of costs and consequences of two or more alternative courses of action.

The ultimate objective of all pharmacoeconomical evaluation methods is to compare the cost and outcome of alternative regimens, ideally by generating a single index or cost-outcome ratio. This ratio can be generated by using the process as shown (Fig. 3.5). The pivotal role of evidence-based medicine in pharmacoeconomic evaluation can be observed from this schematic representation (Li, 2003:194).

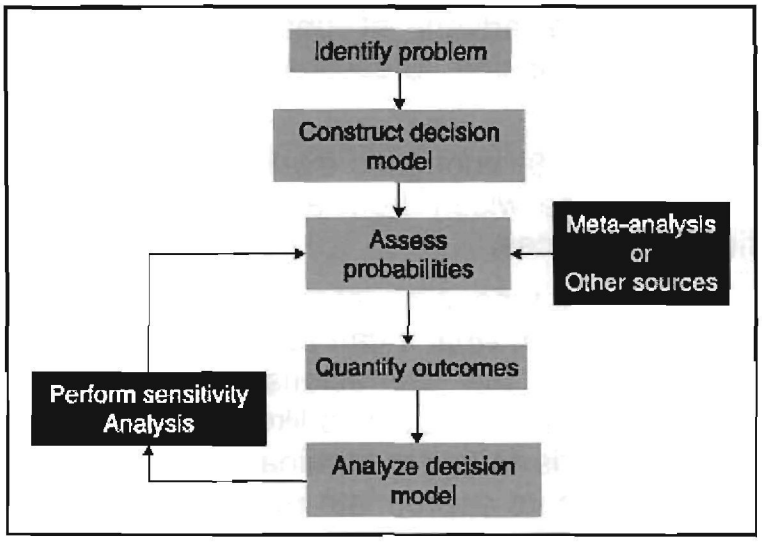

Figure 3.5 Overview of process of pharmacoeconomic evaluation (Li, 2003:194).

According to the WHO (2000:8) the main steps of performing an economic evaluation are:

- defining the economic question and the perspective of the study;
- determining the treatments to be evaluated;
- choosing the study design;
- identifying, measuring and valuing the costs of the alternative treatments;
- identifying, measuring and valuing the benefits of the alternative treatments;
- adjusting costs and benefits for differential timing;
- measuring the incremental costs and benefits;
- putting the costs and benefits together and analysing the results; and
- testing the sensitivity of the results.

3.5.4 Applications of pharmacoeconomic studies

According to Li (2003:194) the pharmacoeconomic field has shown rapid growth in the past decade as health policy makers have faced a continuing series of decisions about funding new clinical therapies in an era of increasingly constrained healthcare resources. Therefore, Miller (2005:1) explains that pharmacoeconomics is vitally important to drug manufacturers in terms of communicating to external decision-makers (payers, prescribers, patients) the value of

their products, achieving regulatory and reimbursement approval and contributing to commercial success. Since development of new drugs is long, costly and risky, and decisions must be made how to allocate considerable research and development (R&D) resources, pharmacoeconomics also has an essential role informing internal decision-making during drug development.

According to Miller (2005:2) pharmacoeconomics can be used to aid resource allocation decisions, which means it can help manufacturers develop more efficient products in a more efficient manner. Thus, they will invest in the right products and can better communicate the costs and consequences of their products to the market.

Economics of healthcare includes not just an assessment of the cost of a new therapy, but an assessment of its overall economic and clinical impact. The discipline of pharmacoeconomics is developed to fulfill this role. Therefore, pharmacoeconomics has been lauded to be of great value in the following areas of healthcare delivery: to improve individual and public health through improved rational decision making; to determine relative values among alternative therapies; to improve system resource allocation; to assess whether care is of high quality; to determine whether interventions work in practice; to assess new diagnostic tests; to determine whether programs represent good value for money (Li 2003:194).

However, to date, the most successful applications of the principles of pharmacoeconomics are in the areas of purchase decision (e.g. decision for formulary inclusion); subsidy decision (e.g. level of subsidy for pharmaceuticals); establishing practice standards (e.g. development of clinical practice guidelines); and assessment of technologies (e.g. medical procedures and technologies) (Li 2003:194).

3.5.5 Types of pharmacoeconomic analyses

3.5.5.1 Cost-effectiveness analysis (CEA)

According to Bootman *et al.* (1996:6) cost-effectiveness is defined as a series of analytical and mathematical procedures which aid in the selection of a course of action from various alternative approaches.

Cost-effectiveness analysis involves a more comprehensive look at drug costs. While cost is measured in monetary terms, effectiveness is determined independently and may be measured in terms of a clinical outcome such as number of lives saved, complications

prevented or diseases cured. Cost-effectiveness analysis thus measures the incremental cost of achieving an incremental health benefit expressed as a particular health outcome that varies according to the indication for the drug (WHO, 2003:26).

A cost-effectiveness analysis can also be defined as a method to determine which program/treatment reaches a given objective at minimum cost (Bootman *et al.*, 1996:7).

According to Edejer *et al.* (2003:5) cost-effectiveness analysis have two uses:

- Firstly, CEA of a wide range of interventions can be undertaken to inform a specific decision-maker. This person faces a known set of resource constraints (budget), a set of options for use in the budget, and a series of other (ethical or political) constraints.
- Secondly, CEA of a wide range of interventions can be undertaken to provide general information on the relative costs and health benefits of different technologies or strategies, which contribute through multiple channels to a more informed debate on resource allocation priorities.

According to McCombs (1998:114S) the limitation of this type of approach is that all life-years are valued equally without adjustments for the quality of life enjoyed by the patient.

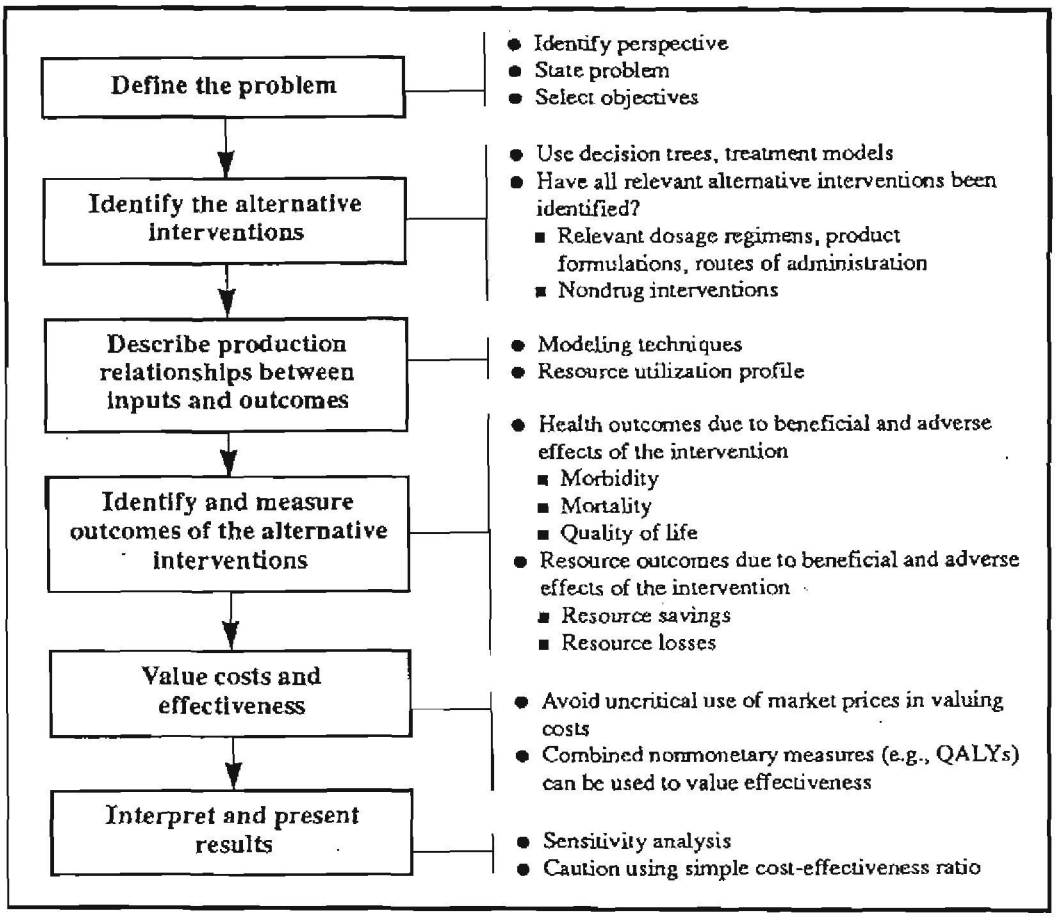

Figure 3.6 Basic steps of cost-effectiveness analysis (Chrischilles, 1996:80).

3.5.5.2 Cost-benefit analysis

According to McCombs (1998:114S) cost-benefit is the most difficult form of clinical economic analysis, which requires that all costs and effects be valued in money.

According to Kitz (1996:103) cost-benefit analysis (CBA) is a method for comparing the value of all resources consumed (costs) in providing a program or intervention with the value of the outcome (benefit) from that program or intervention.

Cost-benefit analysis is used to value both incremental costs and outcomes in monetary terms and therefore allows a direct calculation of the net monetary cost of achieving a health outcome (WHO, 2003:27).

A gain in life-years (survival) may be regarded as the cost of the productive value to society of that life-year using, for example, the average wage. The methods for valuing gains in quality of life include techniques such as *willingness to pay,* where the amount

which individuals would be willing to pay for a quality-of-life benefit is assessed. However, the techniques used to value health outcomes in monetary terms remain somewhat controversial, with the result that cost benefit analysis is so far not widely used in pharmacoeconomic analyses (WHO, 2003:27).

Economic analyses such as those described above may be trial based or modeled. A trial based analysis uses the incremental benefits and use of resources in a clinical trial to calculate an ICER, but this may not be as relevant to the use of the drug as it would be in the marketplace. A modeled analysis is used to apply the benefits and use of resources to a local clinical situation, and to extend the time frame beyond that of a clinical trial. This is particularly important where the benefits of treatment may not be realized until some time in the future. (WHO, 2003:27)

According to Kitz (1996:108) cost-benefit analysis may be applied to single or multiple programs, while cost-effectiveness analysis is only applied to multiple programs. CBA may be used to compare disparate outcomes, while CEA is a method for identifying the least costly approach to achieve a single outcome.

Cost-benefit analysis is usually the most appropriate when a single program is being evaluated, or when funds are limited and budget allocation discussions must be made among programs with unrelated outcomes (Kitz, 1996:108).

3.5.5.3 Cost-minimisation analyses

According to McCombs (1998:114S) cost-minimisation is the most limited type of health economic analysis.

Bootman *et al.* (1996:7) described a cost-minimisation analysis as the examination of costs associated with two or more interventions which demonstrate or is assumed to be equivalent in terms of a given outcome or consequence.

Cost-minimization analysis is a method of calculating drug costs to project the least costly drug or therapeutic modality. Cost minimization also reflects the cost of preparing and administering a dose. This method of cost evaluation is the one used most often in evaluating the cost of a specific drug. Cost minimization can only be used to compare two products that have been shown to be equivalent in dose and therapeutic effect. Therefore, this method is most useful for comparing generic and therapeutic equivalents. In many cases, there is no reliable equivalence between two products and if therapeutic equivalence cannot be demonstrated, then cost-minimization analysis is inappropriate (WHO, 2003:26).

If a new therapy proved to be no safer or more effective than an existing therapy (i.e. there is no incremental benefit), it would normally justify the same price as the existing therapy. This is often not as simple as it may seem, as it requires sound trial-based information on the doses of the two drugs required for equivalent efficacy. An alternative is to use the PDD's for the two drugs in the marketplace to determine the relative prices. This is a pragmatic approach, but assumes that the two drugs are actually used at equally effective doses, and this may not always be the case (WHO, 2003:26).

According to McCombs (1998:114S) a more sophisticated version of the cost-minimisation analyses attempts to measure the net cost of alternative treatments by including in the analysis other health care costs associated with the treatment decision, such as future health care use.

3.5.5.4 Cost-utility analysis

According to Bootman *et al.* (1996:8) cost-utility analysis is an economic tool in which the intervention consequence is measured in terms of patient preference or quality of the healthcare outcome.

Cost-utility analysis is used to determine cost in terms of utilities, especially quantity and quality of life. This type of analysis is controversial because it is difficult to put a value on health status or on an improvement in health status as perceived by different individuals or societies (WHO, 2003:27).

Unlike cost-benefit analysis, cost-utility analysis is used to compare two different drugs or procedures whose benefits may be different. Cost-utility analysis expresses the value for money in terms of a single type of health outcome. The ICER in this case is usually expressed as the incremental cost to gain an extra quality-adjusted life-year (QALY). This approach incorporates both increases in survival time (extra life-years) and changes in quality of life (with or without increased survival) into one measure (WHO, 2003:27).

An increased quality of life is expressed as a *utility* value on a scale of 0 (dead) to one (perfect quality of life). An increased duration of life of one year (without change in quality of life), or an increase in quality of life from 0.5 to 0.7 utility units for five years, would both result in a gain of one quality adjusted life year (QALY). This allows for easy comparison across different types of health outcome, but still requires value judgments to be made concerning increases in the quality of life (utility) associated with different health outcomes. The use of incremental cost-utility ratios enables the cost of

achieving a health benefit by treatment with a drug to be assessed against similar ratios calculated for other health interventions (e.g. surgery or screening by mammography). It therefore provides a broader context in which to make judgments about the value for money when using a particular drug (WHO, 2003:27).

3.5.5.5 Cost-of-illness evaluations

Bootman *et al.* (1996:8) described cost-of-illness analysis as the examination of the overall (direct and indirect) costs of a particular disease. This economic methodology attempts to define all of the costs associated with a particular disease.

3.5.6 Clinical economic models

The heart of most clinical economic evaluations is a medical decision model or decision tree. McCombs (1998:115S) specified that *decision-analytic models have four components:*

- the outcome states possibilities (outcomes) for the disease, fases through which patients must pass and final outcome;
- the transition probabilities between states;
- the realm of the economist; and
- the risk group.

When the first three components is specified for the population as a whole, it becomes possible to compare the costs and effects of alternative treatments

According to Van Den Bos (2006) the primary area in which pharmacoeconomic modelling falls short is in the inability to specify and quantify any medical cost offsets associated with the use of a drug. Furthermore, economic models typically compare the manufacturer's own drug to a single comparator or a placebo.

A more useful model would incorporate all the relevant treatment options for the medical condition of interest in a single head-to-head comparison (Van Den Bos, 2006).

3.5.7 Pharmacoeconomics, randomised controlled trials and healthcare claims data

Clinical trials are used to evaluate the efficacy of therapies. Bootman *et al.* (1996:10-12) describes the relationship between economic evaluations and clinical trials as threefold:

- the pharmacoeconomic evaluation may be a secondary objective of a trial designed primarily for safety and efficacy;

- the pharmacoeconomic evaluation may be the principle purpose of a clinical trial; or
- a pharmacoeconomic evaluation may be done retrospectively on clinical data obtained in previous trials.

Bootman *et al.* (1996:12) explains that pharmacoeconomic evaluation has a different focus than the traditional clinical trial in two respects. Firstly, the economic evaluation is more concerned about extrapolating to what happens in "real life" than under controlled conditions. In other words, the economic study is more interested in effectiveness rather than efficacy. Secondly, the economic study attempts to measure different outcomes. A clinical trial focuses on medical indicators while the economic study is designed to measure the effects on resource consumption, productivity, and/or quality-of-life.

In short, Bootman et al. (1996:13) describes that an economic evaluation may be added as component to a clinical trial with the goal to monitor or estimate:

- Resource consumption: health services and other (direct costs and benefits).
- Lost productivity through morbidity/or premature death (indirect costs and benefits)..
- Quality-of-life or willingness to pay.

3.5.8 Meta-analyses

According to Berlin (1994:525) meta-analysis has been defined as "the statistical analysis of a collection of analytic results for the purpose of integrating the findings".

When conducting pharmacoeconomic and other studies, the sometimes-daunting task of sifting large amounts of contradictory information into an overall assessment of the treatment effect can become a very biased process, especially when a traditional literature review is conducted (Reith & Malone, 2001:594).

Meta-analysis is used to identify sources of variation among study findings, and to provide an overall measure of the effect as a summary of those findings (Berlin, 1994:525).

According to Reith and Malone (2001:594) the summary of a traditional literature review reflects the reviewer's opinion, which may be intuitively correct but lacks the substantiation obtained through formal statistical testing. A meta-analysis study allows statistical integration and combination of information across studies

to quantify the effects of interest. As a result, the meta-analysis becomes a quantitative literature review.

Furthermore, results from a meta-analysis can be incorporated into decision-analysis models to evaluate such issues as the cost-effectiveness of a given therapy (Reith & Malone, 2001:594).

According to Berlin (2004:526) a meta-analysis can be conducted for the following reasons:

- to study uncommon negative outcomes of therapies;
- to explore the reasons for inconsistencies of results across previous studies;
- to investigate the sub-groups of patients in whom therapy may be more or less effective;
- to combine studies involved with the approval process of new therapies; and
- to investigate new indications for existing therapies, particularly when those outcomes are uncommon or the past studies have neen small.

3.5.9 Sensitivity analyses

According to McCombs (1998:116S) the final piece to any good economic analysis is the sensitivity analysis. According to Li (2003:198) sensitivity analysis is a test of the stability of the conclusions of the performed decision analysis over a range of probability estimates, value judgments and structural assumptions.

As Drummond *et al,* as quoted by the WHO (2000:26), suggest, sensitivity analysis may be needed when estimates are subject to debate. This may occur if no estimates are available, the estimates are subject to imprecision, or there is methodological controversy such as those surrounding discount rates. Upper and lower bounds on estimates for the sensitivity analysis can be set by using evidence from other studies, current practice in the literature or by soliciting judgments from those who will be making decisions. Calculations can be made using a combination of best guess, most conservative and least conservative estimates.

Much of the data necessary to completely specify the medical decision analytic model may not be available, thus requiring that gaps in knowledge be filled in by assumptions and expert opinion. A good clinical economics evaluation will clearly identify those assumptions that are critical to the results and test the sensitivity of

the results to changes in these assumptions (McCombs, 1998:116S).

In other words, sensitivity analysis is an investigation into how projected outcome varies along with changes in the key assumptions on which the projections are based. Sensitivity analysis is an integral part of any decision analysis and pharmacoeconomic evaluation as there are always uncertainties in the values of the probabilities of the different clinical outcomes and costs of resource consumption used in the initial analysis (Li, 2003:198).

3.6 Pharmaco-epidemiology

3.6.1 An overview of pharmaco-epidemiology

Epidemiology has been defined by the World Health Organization (2003:8) as the study of the distribution and determinants of health-related states and events in the population, and the application of this study to control health problems.

Einarson *et al.* (1997:372) stated that pharmaco-epidemiology is a relatively new study field, with concepts, methods and applications that have made great contributions to healthcare over the past few decades.

The WHO (2003:8) states that pharmaco-epidemiology applies epidemiological methods to studies of the clinical use of drugs in populations. A modern definition of pharmaco-epidemiology is: the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population, thereby improving health outcomes.

According to Waning and Montagne (2001:4) pharmaco-epidemiology currently focusses on the identifiction of potential or realised drug use problems. Epidemiology provides a theoretical basis for the examination of the source of supply and flow of drugs throughout a population, as well as the effects experienced by patients in the study population.

According to the International Society for Pharmaco-epidemiology (ISPE) (2006) pharmaco-epidemiology borrows from both pharmacology and epidemiology. Thus, pharmaco-epidemiology can be called a bridge science spanning both pharmacology and epidemiology.

Pharmacology is the study of the effect of drugs and clinical pharmacology is the study of effect of drugs in humans. Part of the task of clinical pharmacology is to provide a risk benefit assessment

for the effect of drugs in patients. Doing the studies needed to provide an estimate of the probability of beneficial effects in populations, or the probability of adverse effects in populations and other parameters relating to drug use may benefit from using epidemiological methodology (ISPE, 2006).

Pharmaco-epidemiology may be drug-oriented, emphasising the safety and effectiveness of individual drugs or groups of drugs, or utilisation-oriented aiming to improve the quality of drug therapy through educational intervention (WHO, 2003:8) .

Sophisticated utilisation-oriented pharmaco-epidemiology may focus on the drug (e.g. dose-effect and concentration-effect relationships), the prescriber (e.g. quality indices of the prescription), or the patient (e.g. selection of drug and dose, and comparisons of kidney function, drug metabolic phenotype/genotype, age, et cetera).

Drug utilisation reviews as well as pharmacoeconomic studies are both methods used in pharmaco-epidemiology (Sacristan & Soto, 1994:300). Therefore, drug utilisation research is an essential part of pharmaco-epidemiology as it describes the extent, nature and determinants of drug exposure (WHO, 2003:8).

Drug utilisation studies often employ various sources of information that focus on drugs, while the term epidemiology implies defined populations in which drug use can be expressed in terms of incidence and prevalence (WHO, 2003:8).

Pharmacoepidemiological studies often make useful contributions to our knowledge about effectiveness and safety, because, unlike clinical trials, they assess drug effects in large, heterogeneous populations of patients over longer periods (WHO, 2003:9).

According to Strom (1994:9) pharmacoepidemiologic studies make various valuable contributions to healthcare. The reassurance of drug safety is one of the most important contributions made by pharmaco-epidemiology. Furthermore, pharmaco-epidemiology reassures that the sponsor of the study, whether manufacturer or regulator, is fulfilling the organisational duty ethically and responsibly by looking for any undiscovered problems which may occur (Strom, 1994:9).

3.6.2 The objectives of pharmaco-epidemiology

According to Stewart (1978:122) pharmaco-epidemiology has the following objectives:

- to asses drug use patterns (DUR);
- to document physicians' prescribing habits;

- to assess toxicity of chronic medications;
- to monitor why a drug is being used;
- to monitor the patient who is using the drug;
- to perform drug costs analysis;
- to collect information on new uses of a drug;
- to document the clinical efficacy of drugs; and
- to alert healthcare systems of possible drug-related problems.

3.6.3 Defining evidence-based medicine

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about individual patients. This means integrating individual clinical expertise with the best available external clinical evidence from systematic research. (Bedenoch & Heneghan, 2002:1).

According to Wiffen (1997:510) evidence-based medicine involves finding and interpreting the best evidence available to answer a specific clinical question and implementing findings. Sackett *et al.* (1996:71) describes evidence based medicine as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. The best available external clinical evidence is clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens (Sackett *et al.*, 1996:71).

3.6.4 The objectives and importance of evidence-based medicine

According to Dickersin *et al.* (2007) the term *evidence based medicine* was coined in 1991 by a group at McMaster University, Ontario. It arose from a confluence of events and changes in our culture. Dickersin further states that these include a growing recognition of the following:

- that the systematic synthesis of all dependable information on a topic has greater value than conventional reviews.

- Bias can explain results in many individual studies, and randomised clinical trials are now recognised as the study design that is best suited to avoiding bias in questions of intervention effectiveness, although other types of study may be better for other types of questions.
- Tragedy can result from paying attention to poor quality evidence instead of good quality evidence.
- Clinicians need information, and they don't get enough from the sources they typically use.
- The medical literature is growing exponentially, and there is not enough time in the day to read even the good stuff.
- Undesirable gaps and variation in practice exist.

3.6.5 Assessing the quality of evidence

According to Li (2003:196) it is important to always obtain evidence from the highest possible hierarchy of evidence.

Table 3.2 Hierarchy of evidence (Li 2003:196).

1	**Systematic reviews and meta-analyses** Systematic review is the review of a body of data that uses explicit methods to locate primary studies, and uses explicit criteria to assess their quality. *Meta-analysis is a statistical analysis that combines the results of several independent clinical trials considered to be 'combinable' usually to the level of reanalysing the original data.*
2	**Randomized control trials** Individuals identical for any significant variables are randomly allocated to a control group and a group who receive a specific intervention, and followed up for specific end points.
3	**Cohort studies** Groups of people selected on the basis of their exposure to an agent or risk factor and followed up for specific outcomes.
4	**Case-control studies** A retrospective analysis used to evaluate the differences between the 'cases' (group with the condition) and the 'controls' (matched group without the condition)
5	**Cross sectional surveys** Survey or interview of a sample of the population of interest at one point in time
6	**Case reports** A report of a single patient; sometimes collected together into a short series
7	**Expert opinion** A consensus of experience

3.6.6 Pharmacoepidemiological methods and study designs

A variety of study designs and methods are used to gather pharmacoepidemiologic data. These methods include the following:

- case reports;
- case series;
- case-control studies;
- cohort studies;
- cross-sectional surveys;
- systematic reviews; and
- randomised clinical trials.

3.6.6.1 Case reports

According to Strom (1994:20) a case report describes a single patient who was exposed to a drug and experienced a particular, adverse outcome.

A case report is collections of reports on the treatment of individual patients or a report on a single patient. Because they are reports of cases and use no control groups with which to compare outcomes, they have no statistical validity (DUMC, 2006).

Case reports are useful for the preparation of a hypothesis regarding drug effects, which can be tested with more rigorous study designs (Strom, 1994:20).

3.6.6.2 Case series

A case-series is a report on a series of patients who have the outcome of interest. No control group is involved (Bedenoch & Heneghan, 2002:43). A case series has been described by Strom (1994:20) as collections of patients with a single outcome, whose antecendent exposures are the examined.

A case series can be useful for quantifying the incidence of an adverse reaction, as well as for being certain that any particular adverse effect of concern does not occur in a population which is larger than that studied prior to drug marketing (Strom, 1994:21).

3.6.6.3 Case-control studies

A retrospective analysis comparing subjects with the condition (cases) to those without it (controls) with respect to possible risk or causative factors (Waning *et al*, 2000:5).

According to Badenoch and Heneghan (2002:43) a case-control study involves identifying patients who have the outcome of interest (cases) and control patients without the same outcome, and looking to see if they had exposure of interest. This permits estimation of odds ratios, but not absolute risks (Bedenoch & Heneghan, 2002:55).

Case control studies can be particularly useful during the study of multiple possible causes of a single disease, because you can study any number of exposures as potential risk factors using the same cases and controls (Strom, 1994:23).

The advantages of case-control studies are that they are cheap, quick, and are the only way of studying very rare disorders or those with a long time lag between exposure and outcome. Disadvantages include the reliance on records to determine exposure, difficulty in

selecting control groups, and in eliminating confounding variables (Badenoch & Heneghan, 2002:55).

3.6.6.4 Cohort studies

An incidence study that follows a population free of health problems over time, examining subsequent development of problems and factors associated with them (Waning *et al.*, 2000:5).

A cohort study involves the identification of two groups (cohorts) of patients, one which did receive exposure of interest and one which did not, and following these cohorts forward for the outcome of interest (Badenoch & Heneghan, 2002:44).

Stergachis and Hazlet (1997:67) stated that cohort studies could be either retrospective or prospective.

Cohort studies are cheaper and simpler than randomised clinical trials, can be more rigorous than case-control studies in eligibility and assessment, can establish the timing and sequence of events, and are ethically safe. However, they cannot exclude unknown cofounders, blinding is difficult, and identifying a matched control group may also be difficult (Badenoch & Heneghan, 2002:45).

3.6.6.5 Cross-sectional survey

A cross-sectional survey measures the prevalence of health factors (outcomes and determinants) at appoint in time or over a short period. Cross-sectional studies are relatively cheap and simple to perform, as well as ethically safe. However, they cannot establish causation (only association) and are susceptible to bias (Badenoch & Heneghan, 2002:45).

3.6.6.6 Systematic reviews

A systematic review is an article in which the authors have systematically searched for, appraised, and summarised all of the medical literature for a specific topic (Badenoch & Heneghan, 2002:48).

3.6.6.7 Randomised clinical trials

According to Strom (1994:25) experimental studies are studies in which the investigator controls the therapy that is to be received by each participant. Therfore a randomised clinical trial is performed on randomly allocated patients between or among the study groups.

During a randomised controlled clinical trial (RCT) a group of patients is randomised into an experimental group and a control

group. These groups are followed up for the variables/outcomes of interest (Badenoch & Heneghan, 2002:47).

Randomised clinical trials are the most scientific and ethical method for the investigation of new therapies (Waning & Montagne, 2001:66).

According to Badenoch and Heneghan (2002:55) a RCT is the most powerful method of eliminating confounding variables and permit the most powerful statistical analysis. However, they are expensive, sometimes ethically problematic, and may still be subject to selection and observer bias.

It is important to note that randomised trials cannot contribute to our understanding of rare or long-term side-effects associated with certain therapies (Stergachis & Hazlet, 1997:62).

3.6.7 The future of pharmaco-epidemiology

According to Ström (2006) future scientific developments include: applications of new epidemiological methods, drug utilisation review programs, evaluation of casuality in case reports, systematic screening for adverse drug reactions, appropriate role of data mining, studies of beneficial drug effects, studies of pharmacoeconomics, studies to aid in individualising drug therapy, quality of life studies and large simple trials.

Ström (2006) also predicts that in the future, molecular methods could be used to measure genetics in traditional case-control studies and to measure individuals' probability of drug response.

Future threats for the development of pharmaco-epidemiology include scientific errors, funding limitations, absence of training programs, corruption by studies conducted purely for marketing purposes and inappropriate use in litigation (Ström, 2006).

In South Africa, the submission of Pharmacoeconomic data has also become essential. According to SA (2003:22) the following can be requested by the Authority as the situation warrants when adverse reactions are reported: additional pharmacovigilance data, such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmaco-epidemiology studies, pre-clinical studies, pre-clinical studies or significant product quality data. This will be requested for submission within a time period specified by the Authority.

3.6.8 Applications of pharmacoepidemiologic studies on combination analgesics

For the purpose of this dissertation, the following pharmacoepidemiologic objectives will be utilised:

- Pharmacologic assesment of the drug use patterns (DUR) of combination analgesic medicine items;
- Pharmacoepidemiologic analysis of the costs associated with combination analgesic medicine items.

3.7 Chapter summary

This chapter provided insight into the following health care concepts: the South African private health care system, managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology.

Chapter 4
Empirical investigation

4.1 Introduction

In this chapter the research objectives, research method and design, data source, study population and data analysis of the empirical investigation will be discussed.

4.2 Research objectives

The research objectives were divided into general and specific objectives.

4.2.1 General research objectives

The general objective of this study was to investigate the prescribing patterns of combination analgesics and the cost associated with their usage in a section of the private healthcare sector of South-Africa – utilising a medicine claims database accordingly.

For the purpose of this study combination analgesics were defined as medicine items containing an analgesic active ingredient in combination with other analgesic active ingredients or other ingredients e.g. caffeine, decongestants or antihistamines.

4.2.2 Specific research objectives

This research project consists of two phases, namely a literature review and an empirical investigation.

Firstly the specific objectives of the literature review were the following:

- To conceptualise pain and the treatment protocols thereof from available literature;
- To review combination analgesics and conceptualise the usage from the literature;
- To review the South African health care system; with special reference to the private health care system;
- To conceptualise managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology from the literature; with special reference to the usage of combination analgesics.

Secondly the specific objectives of the empirical investigation were:

- To investigate the prevalence and cost relationship of combination analgesics in relation to all the medicine items on the database;
- To investigate the prevalence and cost relationship of combination analgesics in relation to analgesic medicine items on the database;
- To compare the cost impact of the usage of generic combination analgesics and innovator products;
- To compare the cost-analysis of the different active ingredient combinations;
- To analyse the usage and prescription patterns of different combination analgesics, according to trade names, as well as the costs associated with these drugs according to the database;
- To analyse the average number of combination analgesic prescriptions per patient per year;
- To identify combination therapy of analgesics and determine the costs associated with these combinations;
- To analyse the prevalence of combination analgesics available without prescription;
- To possibly lift out other aspects which may require further investigation.

4.3 Research design

During quantitative research, the researcher may be testing a hypothesis, investigating frequencies of events and quantifying relationships between clearly defined variables (Smith, 2002:113). Quantitative research involves the collection of data within a predetermined and standardised framework devised by, and in accordance with the perspectives of, the researcher (Smith, 2002:182).

In a retrospective study, the outcome of interest has already occurred at the time the study is initiated. A retrospective study design allows the investigator to formulate ideas about possible associations and investigate potential relationships (Nedarc, 2006).

The general objective of this study was to investigate the prescribing patterns of combination analgesics and the cost associated with their usage by reviewing, analysing and interpreting data from a medicine claims database. The patterns of drug utilisation were

determined after the drug had been dispensed and paid for by the pharmacy benefit management company.

Therfore the research design can be classified as a quantitative, retrospective drug utilisation review.

The research design of the study was done by classifying all the combination analgesic items and their equivalent generics in the database into different combinations of active ingredients. The different analgesic combinations studied included the following:

- Aspirin 150mg/ Codeine phosphate 4mg ;
- Aspirin/ Caffeine;
- Aspirin 500mg/ Codeine phosphate 8mg;
- Aspirin 200mg/ Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg;
- Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate;
- Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg;
- Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg;
- Aspirin/ Paracetamol/ Caffeine;
- Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg;
- Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg;
- Ibuprofen 200mg/ Paracetamol 250mg;
- Ibuprofen 400mg/ Paracetamol 325mg;
- Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg;
- Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg;
- Ibuprofen 200mg/ Codeine phosphate 10mg;
- Ibuprofen 200mg/ Paracetamol 350mg;
- Orphenadrine citrate. 35mg/ Paracetamol 450mg;
- Paracetamol 100mg/ Aspirin 400mg/ Caffeine anhydrous 30mg;
- Paracetamol 500mg/Chlormezanone 100mg;

- Paracetamol 120mg/ Codeine phosphate 5mg;
- Paracetamol 320mg/ Codeine phosphate 8mg;
- Paracetamol 500mg/ Codeine phosphate 10mg;
- Paracetamol 500mg/ Codeine phosphate 20mg;
- Paracetamol 500mg/ Codeine phosphate 8mg;
- Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg;
- Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg;
- Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg;
- Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg;
- Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg;
- Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg;
- Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg;
- Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg;
- Paracetamol 120mg/ Doxylamine succinate 5mg;
- Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg;
- Paracetamol 500mg/ Mephenesin 150mg;
- Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg;
- Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg ;
- Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg;
- Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg;
- Propoxyphene HCl 50mg/ Paracetamol 325mg;
- Propoxyphene HCl 65mg/ Paracetamol 250mg; and

- Paracetamol 325mg/ Tramadol 37.5mg

4.4 Research method

Phase 1: The Literature review

The aim of the literature review was to investigate the principles of managed health care, pharmacoeconomics, pharmaco-epidemiology and drug utilisation review, all of which are important to ensure effective and efficient delivery of healthcare.

The literature section also contained extensive information on analgesics, specifically concentrating on combination analgesics and the usage thereof.

Phase 2: The empirical investigation

The empirical investigation consisted of the following components:

- Selection of a research design.
- Selection and composition of the study population.
- Selection and application of criteria and measuring instruments for data analysis.
- Data application and data analysis.
- Reliability and validity of research instruments.
- Report and discussions of the results of the empirical investigation.
- Conclusion and recommendations based on the results of the empirical study as well as the limitations of the study.

4.5 Data source used for the empirical investigation

The data for this study was obtained from *Interpharm Data systems (Pty.) Ltd.*, which offers specialised clinical benefit management solutions to medical schemes (Linux, 2007).

Data were extracted from the central database of *Interpharm Data systems (Pty.) Ltd.*, for a study period of five years from 1 January 2001 to 31 December 2002 and from 1 January 2004 to 31 December 2006. The study period was divided in five one periods. The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for the whole 2003 and therefore the usage and costs of drugs associated with this period cannot be compared with the other periods.

4.6 Study population

The total study population consisted of all the prescriptions claimed through *Interpharm Data Systems (Pty.) Ltd.* during the specific study periods from 2001-2002 and 2004-2006, whilst the study population consisted of all the claimed prescriptions that contained one or more combination analgesics. Neither the name of the prescribing doctor, medical scheme nor the patient's name was revealed, in order to maintain patient confidentiality.

4.7 Database

The database consists of all the prescriptions claimed through *Interpharm Data Systems (Pty.) Ltd* for the study period 1 January 2001 to 31 December 2002 and from 1 January 2004 to 31 December 2006. The following fields were used in the study:

- The Nappi code of the medicine product.
- The description (trade name) of the drug.
- The quantity of the drug that were dispensed.
- The price of the drug.
- The prescription number.
- The date of dispensing.
- Indicator for generic or innovator product.
- Medical scheme name, member and dependent.

4.8 Data analysis

The data were analysed by using different computer software programmes and by applying different classification systems. Specific measuring instruments and statistical analyses have been applied to the data.

4.8.1 Data application and data analysis

The data were analysed by emplementing certain steps. Firstly, specific criteria were applied to the database. The Statistical Analysis System® (SAS institute inc. 2002-2003) was used to extract and analyse certain data from the database. Microsoft Excel 2000® was used to compute certain statistical measures such as the cost-prevalence index.

4.8.2 Classification system used

Various classification systems were used during this study.

4.8.2.1 Nappi code

Every medicine on the medicine claims database has a NAPPI code. The NAPPI code consists of a series of numbers which is unique for every agent and which also distinguishes between different dosage forms of the same agent (Medicredit, 2007). The NAPPI codes of the combination analgesic items were used to acquire the data from the central database and run the queries in SAS 9.1®.

4.8.2.2 The MIMS classification system

This classification system classifies medicine according to its pharmacological action. The MIMS® (Snyman, 2006:11a) classification was used as matrix to classify analgesics according to their pharmacological action.

The MIMS (Snyman, 2006:66) sub-classifies the pharmacological group analgesics (group 3) as follows:

- 3.1 Narcotic analgesics;
- 3.2 Analgesics and antipyretics;
- 3.3 Combinations; and
- 3.4 Other

Analgesic combinations are medicine items which contain two or more active ingredients with analgesic activity.

This classification was also used to run queries in SAS 9.1® (SAS for Windows, 9.1, 2006).

4.8.2.3 Classification of products according to the active ingredient combination

The MIMS® classification constitutes four sub-pharmacological analgesic groups; therefore the analgesic combinations were also classified according to their active ingredient combinations.

4.8.2.4 Classification according to innovator or generic drug

The type of medicine item (innovator or generic) is another criterion under which combination analgesics have been analysed.

An innovator introduces something new for the first time. Thus, an innovator medicine item is a newly introduced product, containing a new active ingredient or combination of active ingredients.

Generic medicine contains exactly the same active pharmaceutical ingredients in the same dosage and in the same dosage form as the original patented medicine item (innovator), at a much lower price (MCC, 2003:1). Generic medicine is manufactured when the patent right of the innovator product has expired and other pharmaceutical companies therefore also have the right to manufacture the same kind of medicine item which does the same work (Medihelp, 2007).

4.8.3 Measuring parameters

4.8.3.1 Prevalence

Prevalence is defined as:

> the ratio (for a given time period) of the number of occurrences of a disease or event, to the number of units at risk in the population (Wordnet, 2007).

Furthermore, it is the:

> probability that a condition exists in a specific population or the probability of the occurrence of a condition (Waning & Montagne, 2002:21).

Prevalence is a statistic of primary interest in public health because it identifies the level of burden of disease or health-related events on the population and health care system (NCI, 2007). According to Manitoba Centre For Health Prevalence (MCHP, 2003), prevalence data might have implications to the provision of services needed in a community.

Prevalence represents new and pre-existing cases alive on a certain date, in contrast to incidence which reflects new cases of a condition diagnosed during a given period of time. Prevalence is a function of both the incidence of the disease and survival (NCI, 2007).

In this study the prevalence of the following medicine items will be analysed as follows:

- The prevalence of all medicine items of the total database claimed during the study period e.g. the total number of prescriptions or medicine items on the total database.
- The prevalence of the pharmacological group, e.g. combination analgesic medicine items claimed during the study period.
- The prevalence of innovator and generic combination analgesics medicine items claimed during the study period.
- The prevalence of individual combination analgesic medicine items e.g. Myprodol® capsules that contain different active

ingredient combinations e.g. paracetamol, codeine phosphate and ibuprofen.

4.8.3.2 Economic impact and cost-minimisation

The daily cost of treatment (as reflected by the cost per defined daily dose) is a recognised unit of measurement in drug utilisation studies (Truter, 1997:19). The treatment cost per day, plus the remaining costs (direct and indirect), can be used in any type of pharmacoeconomic study, particularly in cost-minimisation studies. Comparisons of the total cost of a drug or therapeutic class of drugs between geographical areas can also be carried out (Truter, 1997:19). In this study the geographical areas as well as demographic information such as age and gender were not available on the database and is one of the limitations of this study.

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

- The total cost of all medicine items claimed during the five study periods was compared.
- The total cost of all combination analgesic medicine items claimed during the five study periods were compared for the different time periods.
- The cost difference between innovator and generic combination analgesics medicine items claimed.
- The cost of individual combination analgesic medicine items e.g. Myprodol® capsules that contain different active ingredient combinations e.g. paracetamol, codeine phosphate and ibuprofen.

4.8.4 Statistical analysis

The following statistical methods were used to analyse the data.

4.8.4.1 Arithmetic mean

The arithmetic mean is the most common measure of central tendency (Panneerselvam, 2006:39).

In mathematics and statistics, the arithmetic mean (or simply the mean) of a list of numbers is the sum of all the members of a list divided by the number of items in the list (Wikipedia, 2007a).

According to Steyn *et al.* (1994:99) the arithmetic mean (or average) of a set of observations is defined by

Where:

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

$\bar{x}$ = mean.
x = the values of the variable.
Σ = the sum of.
n = the number of observations.

4.8.4.2 Standard deviation

The standard deviation is the most frequently calculated measure of variability. The standard deviation value represents the average distance of a set of scores from the mean (Barlo, 2007).

According to Barlo (2007) the standard deviation is the root mean square deviation of the values from their arithmetic mean

Where:

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

$\bar{x}$ = the mean.
s = standard deviation.
Σ = sum of.
x = any value in the data set.
n = the number of observations.

4.8.4.3 Cost prevalence index

The cost-prevalence index (CPI) can be defined as follows (Serfontein, 1989:180).

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

In context of the study the cost index can be interpreted as follows:

- If the cost-prevalence index is < 1 then the medicine therapy utilised is relatively inexpensive in comparison with other therapies.
- If the cost-prevalence index = 1 then there is equilibrium between the costs and prevalence of the medicine therapy.
- If the cost-prevalence index is > 1 then the therapy utilised is expensive.

4.8.4.4 Effect sizes/d-values

Effect size is a measure of the strength of the relationship between two variables (Wikipedia, 2007b).

The effect size can be calculated by the following formula:

$$d = \frac{\bar{x} - \bar{x}}{S\,max}$$

Where:

$\bar{x}$ = the average medicine treatment cost of a (e.g. combination analgesic a)

$\bar{x}$ = the average medicine treatment cost of b (e.g. combination analgesic b)

Smax = the maximum standard deviation between a and b

d = effect size

Cohen, as quoted by the UCCS (2000), defined *d* as the difference between two means, divided by standard deviation, s, of either group.

Cohen, as quoted by the UCCS (2000), hesitantly defined effect sizes as:

- small, $|d| = 0.2$;
- medium, $|d| = 0.5$; and
- large, $|d| = 0.8$.

Therefore, the only d-values greater than, or equal to 0.8, will be assumed to have practical significant value and will be discussed in chapter 5.

The effect size will be used to determine whether there is any practically significant difference between the average medicine treatment costs for different types of combination analgesics.

4.9 Reliability and validity

The data for analysis were directly obtained from a medicine claims database, *Interpharm Data systems (Pty.)*. Therefore, direct manipulation of the data by the researcher was impossible. The research was conducted assuming that all the data would be correct.

The data obtained and analysed from the data source for the five year period (1 January 2001 to 31 December 2002 and 1 January 2004 to 31 December 2006) can only be generalised to the database and the specific study population.

4.10 Ethical aspects

Data for the analysis were obtained from one medicine claims database, thus, limiting external validity, implying that results can only be generalised to the specific database used, as well as to the specific study population. Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the medical scheme administrator providing the data to ensure confidentiality. Thus no specific patient, medical practice, pharmacy or medical scheme could be identified. Thus confidentiality of information was maintained throughout the study.

The data used in this study was analysed with permission from the Pharmacy Benefit Management (PBM) company, utilising *Interpharm Data systems (Pty.) Ltd.* database.

4.11 Results and discussion

The results of the empirical investigation will be discussed in Chapter 5.

4.12 Conclusions and recommendations

The conclusions and recommendations based on the results of the literature review and the empirical investigation will be discussed in Chapter 6.

4.13 Chapter summary

In this chapter the research methodology was discussed. The research objectives, research method and design, data source,

study population and data analysis of the empirical investigation was discussed.

The results and recommendations of the empirical investigation will be discussed in chapter 5.

Chapter 5
Results and discussion

5.1 Introduction

In this chapter, the results of the empirical investigation of the prescribing patterns and cost of analgesics, in particular combination analgesics medicine items for the study periods 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, 1 January 2004 to 31 December 2004, 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006 will be outlined and discussed.

For the purpose of this study, the total database was analysed and the analgesic medicine items have been referred to as medicine items of the main pharmacological group (pharmacological group 3 according to the MIMS® classification system). The combination analgesic items have been referred to as medicine items of the sub-pharmacological group (group 3.3 according to the MIMS® classification system) and have been divided into forty-two different combinations.

Due to the nature and extent of this study, the focus of this study was on combination analgesic medicine items.

5.1.1 Terms and definitions

For the purpose of this study, the following terms and definitions were used:

- *Generic medicine items*

Generic medicine contains exactly the same active pharmaceutical ingredients in the same dosage (strength) and in the same dosage form as the original patented medicine item (innovator), at a much lower price (MCC, 2003:1). Generic medicine is manufactured when the patent right of the original product has expired and other pharmaceutical companies therefore also have the right to manufacture the same kind of medicine item which does the same work (Medihelp, 2007).

A generic medicine item is "a medicine item, which is registered in South Africa, but has never been protected by patent legislation.

Such medicines are being manufactured by companies other than the company that originally held the patent" (SA, 2006:9).

Thus, generics are assumed to be identical in dose, strength, route of administration, safety, efficacy, and intended use (Wikipedia, 2007).

- *Innovator medicine items*

An innovator introduces something new for the first time (Wikipedia, 2007). Thus, an innovator medicine item is a newly introduced product, containing a new active ingredient or combination of active ingredients. An innovator or originator medicine has been defined by SA (2006:8) as:

> a medicine, registered in South Africa, where such medicine is currently protected by patent or has been protected by a patent previously.

- *Medicine items*

Medicine items are agents or preparations which contain at least one active ingredient and is used to prevent or treat an illness.

- *Number of prescriptions*

It refers to the number of prescriptions claimed during a specific period. A prescription is a written instruction from a legal prescriber.

- *Patient*

A patient is someone receiving medication on prescription by a legal prescriber during the study period.

- *Total database or total population*

All the prescriptions on the database claimed during the specific study period.

- *Study population*

The study population in this study represented all records of combination analgesic prescribing during the study period.

- *Analgesic mono-therapy*

Analgesic mono-therapy refers to prescriptions which contained only one analgesic medicine item from pharmacological group 3 according to the MIMS® classification system. Some of these analgesic medicine items can contain more than one active ingredient.

- *Analgesic double-therapy*

Analgesic double-therapy refers to prescriptions which contained two analgesic medicine items from pharmacological group 3 according to the MIMS® classification system.

- *Analgesic triple-therapy*

Analgesic triple-therapy refers to prescriptions which contained three analgesic medicine items from pharmacological group 3 according to the MIMS® classification system.

- *Four analgesics in combination therapy*

Four analgesics in combination therapy refers to prescriptions which contained four analgesic medicine items from pharmacological group 3 according to the MIMS® classification system

- *Five analgesics in combination therapy*

Five analgesics in combination therapy refers to prescriptions which contained five analgesic medicine items from pharmacological group 3 according to the MIMS® classification system.

5.1.2 Points of interest applicable to the scope of this study with the interpretation of the results.

For the purpose of this study, there were five study periods. The following time periods will be denoted in the discussion as follows: 1 January 2001 to 31 December 2001=2001, 1 January 2002 to 31 December 2002 = 2002, 1 January 2004 to 31 December 2004 = 2004, 1 January 2005 to 31 December 2005 = 2005 and 1 January 2006 to 31 December 2006 = 2006.

- The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for this period and thus the usage and costs of drugs associated with this period cannot be compared with the other periods.
- The values of the data that were used have been "rounded-off" to two decimals and may not add up to 100 percent.
- For the purpose of this study, prevalence and frequency will be regarded as the same. Both refer to the number of times a certain value occurs in a set of data.
- It is assumed that all the data obtained from the database is correct.

5.2 General prescribing patterns

General prescribing patterns for the years 2001, 2002, 2004, 2005 and 2006.

Table 5.1 gives the prescribing patterns of the total database, of analgesic medicine items and of combination analgesic medicine items for the five study years, 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, 1 January 2004 to 31 December 2004, January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006.

Table 5.1 General prescribing patterns of the total database, of analgesic medicine items and of combination analgesic medicine items for the years 2001-2002 and 2004-2006.

Description	2001			2002			2004		
	Total database	Analgesics	Combination analgesics	Total database	Analgesics	Combination analgesics	Total database	Analgesics	Combination analgesics
Total number of prescriptions containing at least one medicine item	1475380	305126	258544	2076236	384681	313760	2595242	465193	376513
Total number of medicine items prescribed	2951326	323361	261907	4042145	394432	317997	5305846	477713	381809
Average number of medicine items per prescription	2 ± 1.17	1.03 ± 0.16	1.01 ± 0.11	1.95 ± 1.17	1.03 ± 0.16	1.01 ± 0.12	2.04±1.27	1.03 ± 0.17	1.01 ± 0.12
Total number of innovator medicine items prescribed	2160778	207634	184299	2896367	237957	206124	3525282	282200	241664
Total number of generic medicine prescribed	790548	115727	77608	1145778	156475	111873	1780564	195513	140145
Total cost (R)	379708489.00	20980439.81	18798202.42	601350325.00	28022309.02	24654906.68	661221000.00	25149035.88	21288560.33
Average cost per prescription (R)	257.36 ± 271.06	66.51 ± 71.88	72.71 ± 63.29	289.63 ± 351.05	72.85 ± 93.88	78.58 ± 68.87	254.78 ± 397.84	54.06 ± 76.50	56.54 ± 52.97
Average cost per medicine item (R)	128.66 ± 151.97	64.88 ± 68.55	71.77 ± 61.67	148.77 ± 205.25	71.04 ± 89.76	77.53 ± 67.23	124.62 ± 228.55	52.64 ± 69.06	55.76 ± 51.75
Average cost of innovator medicine items per prescription (R)	151.06 ± 167.83	83.04 ± 77.41	86.54 ± 65.97	176.93 ± 231.84	91.49 ± 107.57	94.96± 74.14	155.80 ± 270.06	69.36 ± 82.66	69.78 ± 57.80
Average cost of generic medicine items per prescription (R)	67.43 ± 64.14	32.30 ± 26.95	36.71 ± 27.43	77.57 ± 75.27	39.96 ± 33.32	45.43 ± 33.58	62.88 ± 74.29	28.52 ± 28.36	31.58 ± 24.72
Minimum cost per item (R)	0.01	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01
Maximum cost per item (R)	51227.67	3485.04	1393.76	56163.92	10014.30	1907.18	92097.44	4490.78	1411.04

Table 5.1 (continued) General prescribing patterns of the total database, of analgesic medicine items and of combination analgesic medicine items for the years 2001-2002 and 2004-2006.

Description	2005			2006		
	Total database	Analgesics	Combination analgesics	Total database	Analgesics	Combination analgesics
Total number of prescriptions containing at least one medicine item	1621739	341591	277088	996787	229980	184744
Total number of medicine items prescribed	3606992	351335	281590	2370572	236356	187745
Average number of medicine items per prescription	2.22 ± 1.37	1.03 ± 0.17	1.02 ± 0.13	2.38 ± 1.44	1.03 ± 0.17	1.02 ± 0.13
Total number of innovator medicine items prescribed	2330359	180699	156995	1416011	74885	63145
Total number of generic medicine prescribed	1276633	170636	124635	954561	161471	124600
Total cost (R)	405829097.00	16818074.72	14265812.95	279160832.00	10636313.51	8791228.57
Average cost per prescription (R)	250.24 ± 403.60	49.23 ± 63.83	51.48 ± 44.84	280.06 ± 434.37	46.25 ± 68.56	47.59 ± 44.53
Average cost per medicine item (R)	112.51 ± 226.99	47.87 ± 60.77	50.66 ± 43.77	117.76 ± 237.81	45.00 ± 64.94	46.83 ± 43.41
Average cost of innovator medicine items per prescription (R)	143.27 ± 272.21	65.22 ± 76.96	64.42 ± 50.93	152.04 ± 294.67	68.41 ± 103.59	63.79 ± 61.39
Average cost of generic medicine items per prescription (R)	56.37 ± 73.74	29.49 ± 25.97	33.34 ± 22.90	66.91 ± 85.48	34.15 ± 28.71	38.23 ± 26.65
Minimum cost per item (R)	0.01	0.01	0.01	0.01	0.01	0.05
Maximum cost per item (R)	69555.01	6566.76	1008.73	56672.89	5991.37	1118.79

5.2.1 Total number of prescriptions/ medicine items claimed

5.2.1.1 Total number of prescriptions/ medicine items claimed

The ***total number of prescriptions*** containing at least one medicine item of the ***total database*** increased with 40.73% (n=600 856) from 2001 to 2002 and with 25% (n=519 018) from 2002 to 2004. From 2004 to 2005 there was a decrease of 37.51% (n=973 515) and from 2005 to 2006 there was a further decrease of 38.54% (n=624 952) (refer to table 5.1).

Table 5.1 indicates that the ***total number of medicine items*** claimed for the **total database** increased with 36.96% (n=1 090 819) from 2001 to 2002 and with 31.26% (n=1 263 701) from 2002 to 2004. From 2004 to 2005 the total number of medicine items claimed for the total database decreased with 32.02% (n=1 698 854) and from 2005 to 2006 there was a further decrease of 34.28% (n=1 236 420) (refer to table 5.1).

The decrease in the ***total number of prescriptions*** containing at least one medicine item and the ***total number of medicine items*** claimed of the ***total database*** from 2004 to 2006 might be due to a decrease in the number of medical aids claimed through the medical schemes administrator from 80 to 35 from 2004 to 2005 and from 68 to 35 from 2005 to 2006.

5.2.1.2 Total number of *analgesic* prescriptions/ medicine items claimed

The ***number of prescriptions*** containing at least one ***analgesic medicine item*** represented 20.68% (n=305 126) in 2001, 18.53% (n=384 681) in 2002, 17.92% (n=465 193) in 2004, 21.06% (n=341 591) in 2005 and 23.07% (n=229 980) in 2006 of the ***total number of prescriptions*** claimed for the corresponding year (N=1 475 380 for 2001, N=2 076 236 for 2002, N= 2 595 242 for 2004, N=1 621 739 for 2005 and N=996 787 for 2006) (refer to table 5.1).

The ***number of analgesic medicine items*** represented 10.96% (n=323 361) during 2001, 9.76% (n=394 432) during 2002, 9.00% (n=477 713) during 2004, 9.74% (n=351 336) during 2005 and 9.97% (n=236 356) during 2006 of the ***total number of medicine items*** claimed for the corresponding year (N=2 951 326 for 2001, N=4 042 145 for 2002, N=5 305 846 for 2004, N=3 606 992 for 2005 and N=2 370 572 for 2006) (refer to table 5.1).

The increased ***percentage of prescriptions containing at least one analgesic medicine item*** and the ***percentage analgesic medicine items*** claimed from 2004 to 2006 is probably a result of the increased availability of generic analgesic medicine items because of the expiry of patents during this period and the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The ***total number of prescriptions*** containing at least one ***analgesic medicine item*** increased with 26.07% (n=79 555) from 2001 to 2001, with 20.93% (80 512) from 2002 to 2004, and decreased with 26.57% (n=123 602) from 2004 to 2005 and with 32.67% (n=123 602) from 2005 to 2006 (refer to table 5.1).

The ***total number of analgesic medicine items*** claimed increased with 21.98% (n=71071) from 2001 to 2002 and with 21.11% (n=83281) from 2002 to 2004. From 2004 to 2005 the total number of analgesic medicine items claimed for the total database decreased with 26.45% (n=126377) and from 2005 to 2006 with 32.73% (n=114 980) (refer to table 5.1).

The prevalence of combination analgesics decreased from 2001 to 2004 and increased between 2004 and 2006. The change in prevalence could be due to an increased availability of generic combination analgesic drugs, at a lower cost.

5.2.1.3 Total number of *combination analgesic* prescriptions/ medicine items

The ***number of prescriptions containing at least one combination analgesic medicine item*** represented 17.52% (n=258 544) during 2001, 15.11% (n=313 760) during 2002, 14.51% (n=376 513) during 2004, 17.09% (n=277 088) during 2005 and 18.53% (n=184 744) during 2006 of the ***total number of prescriptions*** claimed for the corresponding year (N=1 475 380 for 2001, N=2 076 236 for 2002, N=2 595 242 for 2004, N=1 621 739 for 2005 and N=996 787 for 2006) (refer to table 5.1).

The ***number of combination analgesic medicine items*** represented 8.87% (n=261 907) during 2001, 7.87% (n=317 997) during 2002, 7.20% (n=381 809) during 2004, 7.81% (n=281 590) during 2005 and 7.92% (n=187 745) during 2006 of the ***total number of medicine items*** claimed (N=2 951 326 for 2001, N=4 042 145 for 2002, N=5 305 846 for 2004, N=3 607 000 for 2005 and N=2 370 572 for 2006) (refer to table 5.1).

The increased percentage of prescriptions containing at least one combination analgesic medicine item and percentage combination

analgesic medicine items claimed from 2004 to 2006 is probably a result of an increased availability of combination analgesic medicine items.

The ***total number of prescriptions*** containing at least one ***combination analgesic medicine item*** increased with 21.35% (n=55 216) from 2001 to 2002 and with 20.00% (n=62 753) from 2002 to 2004. From 2004 to 2005 there was a decrease of 26.41% and from 2005 to 2006 a decrease of 33.33% (n=92 344) (n=99 425) (refer to table 5.1).

The ***total number of combination analgesic medicine items*** claimed increased with 21.42% (n=56 090) from 2001 to 2002 and with 20.07% (n=63 812) from 2002 to 2004. From 2004 to 2005 there was a decrease of 26.25% (n=100 219) and from 2005 to 2006 a decrease of 33.33% (n=93 845) (refer to table 5.1).

The decrease in the ***total number of prescriptions*** containing at least one ***combination analgesic medicine*** item and the ***total number of combination analgesic medicine items*** claimed of the ***total database*** from 2004 to 2006 might be due to a decrease in the number of medical scheme members because the number of medical schemes claimed through Interpharm® Datasystems decrease from 80 to 35 from 2004 to 2006.

The ***number of combination analgesic medicine items*** represented 81.00% (n=261907) during 2001, 80.62% (n=317997) during 2002, 79.92% (n=381809) during 2004, 80.15% (n=281590) during 2005 and 79.43% (n=187 745) during 2006 of the ***total number of analgesic medicine items*** claimed through the ***total database*** (N=323 361 for 2001, N=394 432 for 2002, N=477 713 for 2004, N=351 336 for 2005 and N=236 356 for 2006) (refer to table 5.1).

5.2.2 Average number of medicine items per prescription

The average number of medicine items per prescription per study year, the average number of analgesic medicine items per prescription per study year and the average number of combination analgesic medicine items per prescription per study year showed a relatively small increase (Refer to table 5.2).

Table 5.2 indicates that the average number of combination analgesic medicine items per prescription stayed relatively constant over the study period with values ranging from 1.01 ± 1.11 combination analgesic medicine items per prescription during 2001 and 1.02 ± 0.13 during 2006.

Table 5.2 The average number of medicine items per prescription (extraction from table 5.1)

Description	2001	2002	2004	2005	2006
Average number of medicine items per prescription on the **total database**	2 ± 1.17	1.95 ± 1.17	2.04±1.27	2.22 ± 1.37	2.38 ± 1.44
Average number **analgesic** medicine items per prescription.	1.03 ± 0.16	1.03 ±0.16	1.03 ± 0.17	1.03 ± 0.17	1.03 ± 0.17
Average number of **combination analgesic** medicine items per prescription.	1.01 ± 0.11	1.01 ± 0.12	1.01 ± 0.12	1.02 ± 0.13	1.02 ± 0.13

The effect sizes (d-values) calculated between the average number of medicine items per prescription for *all medicine items,* for *analgesic medicine items* and for *combination analgesic medicine items* on the *total database* for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005, 2005 to 2006 and 2001 to 2006 were of no practical significance (d<0.8) (refer section 4.7.4.5).

5.2.3 Average cost per prescription

Table 5.3 indicates the increasing trends in the average cost per prescription from 2001 to 2002, and a decreasing trend from 2002 to 2006.

Table 5.3 The average cost per prescription (extraction from table 5.1)

Description	2001	2002	2004	2005	2006
Average cost per prescription of the **total database** (R)	257.36 ± 271.06	289.63 ± 351.05	254.78 ± 397.84	250.24 ± 403.60	280.06 ± 434.37
Average cost per prescription of **analgesics** (R)	66.51 ± 71.88	72.85 ±93.88	54.06 ± 76.50	49.23 ± 63.83	46.26 ± 68.87
Average cost per prescription of **combination analgesics** (R)	72.71 ± 63.29	78.58 ± 68.87	56.54 ± 52.97	51.48 ± 44.84	47.59 ± 44.53

The decrease in the average cost per prescription containing an analgesic or combination analgesic medicine item from 2004 to 2006 may be the result of the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30) and the implementation of the new pricing regulations during May 2004 (Tshabalala-Msimang, 2004:5). Generic medicine items were less expensive than innovator products, therefore the increase from 29.63% (n=77 608) to 66.37% (n=124 600) in the number of generic combination analgesic medicine items claimed between 2001 to 2006 may be the cause of the decrease in the average cost per prescription (refer to Section 5.2.5.3).

The effect sizes (d-values) calculated between the average cost per prescription for ***all medicine items,*** for ***analgesic medicine items*** and for ***combination analgesic medicine items*** on the ***total database*** for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005, 2005 to 2006 and 2001 to 2006 were of no practical significance (d<0.8) (refer to section 4.7.4.5).

5.2.4 Average cost per medicine item

Table 5.4 indicates an increasing trend in average cost per medicine item from 2001 to 2002, and a decreasing trend from 2002 to 2006.

Table 5.4 The average cost per medicine item (extraction from table 5.1)

Description	2001	2002	2004	2005	2006
Average cost per medicine item of the **total database** (R)	128.66 ± 151.66	148.77 ± 205.25	124.62 ± 228.55	112.51 ± 226.99	117.76 ± 237.81
Average cost per **analgesic** medicine item (R)	64.88 ± 68.55	71.04 ± 89.76	52.64 ± 69.06	47.87 ± 60.77	45.00 ± 64.94
Average cost per **combination analgesics** medicine item (R)	71.77± 61.67	77.53 ± 67.23	55.76 ± 51.75	50.66 ± 43.77	46.83 ±43.41

The decrease in the average cost per analgesic or combination analgesic medicine item from 2004 to 2006 may be the result of the implementation of the Generic Substitution Guidelines (South Africa, 2003: MAE30) in April 2003 and the implementation of the new pricing regulations during May 2004 (Tshabalala-Msimang, 2004:5) (refer to section 3.2.7).

The effect sizes (d-values) calculated between the average cost per medicine item for ***all medicine items,*** for ***analgesic medicine items*** and for ***combination analgesic medicine items*** on the ***total database*** for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005, 2005 to 2006 and 2001 to 2006 were of no practical significance (d<0.8) (refer section 4.7.4.5).

5.2.5 Number of innovator/ generic medicine items prescribed

5.2.5.1 Number of all innovator/ generic medicine items prescribed

Table 5.4 indicated a gradual decrease in the ***percentage innovator medicine items*** claimed. Innovator medicine items represented 73.21% (n=2 160 778) of all medicine items claimed during 2001, 71.65 % (n=2 896 367) during 2002, 66.44% (n=3 525 282) during 2004, 64.61% (n=2 330 359) during 2005 and 59.73%

(n=1 416 011) during 2006 (N=2 951 326 for 2001, N=4 042 145 for 2002, N=5 305 846 for 2004, N=3 607 000 for 2005 and N=2 370 572 for 2006) (refer to fig 5.1).

Table 5.4 indicates that *generic medicine items* increased gradually from 26.79% (n=790548) of all medicine items claimed during 2001, to 28.35% (n=1145778) during 2002, to 33.56% (n=1780564) during 2004, to 35.39% (n=1276633) during 2005 and to 40.27% (n=954561) during 2006 (N=2 951 326 for 2001, N=4 042 145 for 2002, N=5 305 846 for 2004, N=3 607 000 for 2005 and N=2 370 572 for 2006).

The increased percentage of generic medicine items is the result of an increased availability of generic medicine items as well as the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The total number of ***innovator medicine items*** on the ***total database*** increased with 34.04% (n=735589) and with 21.71% (n=628915) from 2002 to 2004. From 2004 to 2005 the total number of innovator medicine items on the total database decreased with 33.90% (n=1194923) and with 39.24% (n=914 348) from 2005 to 2006 (refer to table 5.1).

This indicates an increase of the total number of ***generic medicine items*** **in the** ***total database*** of 44.93% (n=355230) from 2001 to 2002 and 55.40% (n=634786) from 2002 to 2004. From 2004 to 2005 the generic products of the total database decreased with 28.31% (n=503931) and with 25.23% (n=32 2072) from 2005 to 2006 (refer to table 5.1).

The decreasing trend from 2004 to 2006 of the number of generic and innovator medicine items may be due to a decrease in the number of medical aids from 80 to 35 from 2004 to 2006.

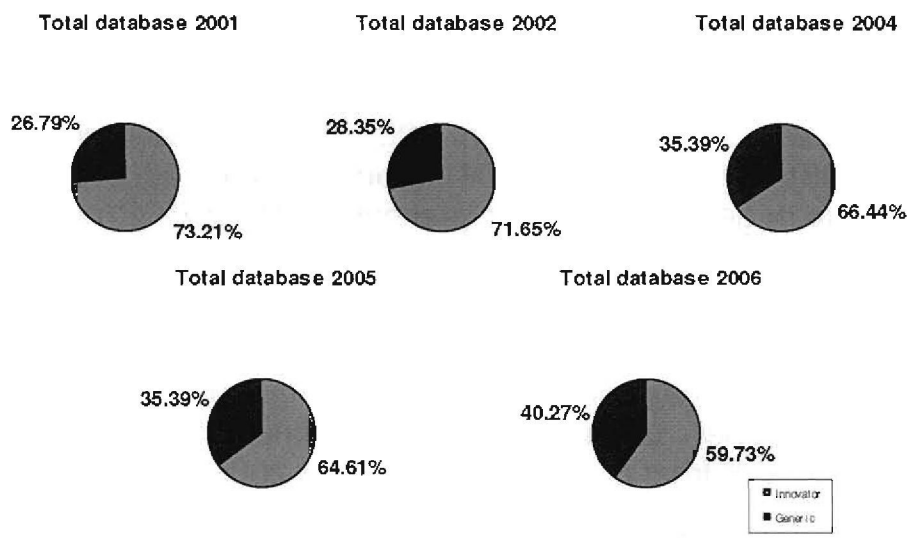

Figure 5.1 The percentage of innovator or generic medicine items claimed for the different study periods.

5.2.5.2 Number of innovator/ generic *analgesic* medicine items prescribed

Innovator analgesic medicine items represented 64.21% (n=184 299) during 2001, 60.33% (n=206 124) during 2002, 63.29% (n=241 664) during 2004, 51.43% (n=156 995) during 2005 and 31.68% (n=74 885) of the ***total number of analgesic medicine items*** prescribed (N=323 361 for 2001, N=394 432 for 2002, N=477 713 for 2004, N=351 336 for 2005 and N=236 356 for 2006) (refer to table 5.5).

Generic analgesic medicine items represented 35.79% (n=115 727) during 2001, 39.67% (n=156 475) during 2002, 40.93% (n=195 513) during 2004, 48.57% (n=170 636) during 2005 and 33.63% (n=161 741) during 2006 of the ***total number of analgesic medicine items*** prescribed (N=323 361 for 2001, N=394 432 for 2002, N=477 713 for 2004, N=351 336 for 2005 and N=236 356 for 2006) (refer to table 5.5).

The increased percentage of generic analgesic medicine items might be the result of the increased availability of generic medicine items on the South African market as well as the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The total ***number of innovator analgesic medicine*** items increased with 14.60% (n=30 323) from 2001 to 2002 and with 18.59% (n=44 243) from 2002 to 2004. From 2004 to 2005 the total number of innovator analgesic medicine items decreased with

35.97% (n=101 500) and from 2005 to 2006 with 58.56% (n=105 815) (refer to table 5.1).

The total ***number of generic analgesic medicine items*** increased with 35.21% (n=40748) from 2001 to 2002 and with 24.95% (n=39038) from 2002 to 2004. From 2004 to 2005 there was a decrease in generic analgesic prescribing of 12.72% (n=24877) and from 2005 to 2006 a decrease of 5.37% (n=9 165) (refer to table 5.1).

The decreasing trend from 2004 to 2006 of the number of generic and innovator analgesic medicine items may be due to a decrease in the number of medical aids claimed through Interpharm Datasystems® from 80 to 35 from 2004 to 2006.

5.2.5.3 Number of innovator/ generic *combination analgesic* medicine items prescribed

Innovator combination analgesic medicine items represented 70.37% (n=184 299) during 2001, 64.82% (n=206 124) during 2002, 63.29% (n=241 664) during 2004, 55.75% (n=156 995) during 2005 and 33.63% (n=63 145) for 2006 of all combination analgesic medicine items claimed (N=261 907 for 2001, N=317 997 for 2002, N=381 809 for 2004, N=381 590 for 2005 and N=187 745 for 2006) (refer to Table 5.5 and Figure 5.2).

Generic combination analgesic medicine items represented 29.63% (n=77 608) during 2001, 35.18% (n=111 873) during 2002, 36.71% (n=140 145) during 2004, 44.25% (n=124 635) during 2005 and 66.37% (n=124 600) during 2006 of all combination analgesic medicine items claimed (N=261 907 for 2001, N=317 997 for 2002, N=381 809 for 2004, N=381 590 for 2005 and N=187 745 for 2006) (refer to Table 5.1 and Figure 5.2).

The increased percentage of generic combination analgesic medicine items might be the result of the increased availability of generic medicine items as well as the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The total number of ***innovator combination analgesic medicine*** items increased with 11.84% (n=21 825) from 2001 to 2002 and with 17.24% (n=35 540) from 2002 to 2004. From 2004 to 2005 the total number of innovator combination analgesic medicine items decreased with 35.04% (n=84 669) and with 59.78% (n=93 850) from 2005 to 2006 (refer to Table 5.1).

The ***generic combination analgesic medicine items*** increased with 44.15% (n=34 265) from 2001 to 2002 and with 25.27% (n=28

272) from 2002 to 2004. From 2004 to 2005 there was a decrease in generic combination analgesic prescribing of 11.07% (n=15 510) and from 2005 to 2006 a decrease of 0.03% (n=35) (refer to Table 5.1).

The decreasing trend from 2004 to 2006 of the number of generic and innovator combination analgesic medicine items may be due to a decrease in the number of medical aids from 80 to 35 from 2004 to 2006.

Table 5.5 Comparison between the percentage of innovator and generic medicine items

Period	Innovator or Generic	Total database (%*)	Analgesic medicine items (**)	Combination analgesic items (%@)
2001	Innovator	73.21	64.21	70.37
	Generic	26.79	35.79	29.63
2002	Innovator	71.65	60.33	64.82
	Generic	28.35	39.67	35.18
2004	Innovator	66.44	59.07	63.29
	Generic	33.56	40.93	36.71
2005	Innovator	64.61	51.43	55.75
	Generic	35.39	48.57	44.25
2006	Innovator	59.73	31.65	33.63
	Generic	40.27	68.35	66.37

%* The total number of innovator or generic medicine items claimed for the specific study period divided by the total number of medicine items claimed for the corresponding period multiplied by hundred.

** The total number of innovator or generic *analgesic medicine items* claimed for the specific study period divided by the total number of analgesic medicine items claimed for the corresponding period multiplied by hundred.

%@ The total number of innovator or generic *combination analgesic medicine items* claimed for the specific period divided by the total number of combination analgesic medicine items claimed for the corresponding period multiplied by hundred.

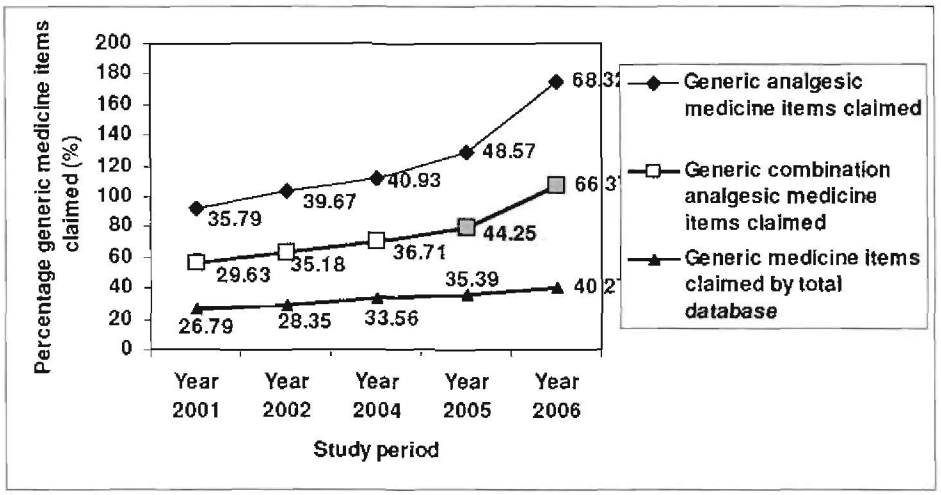

Figure 5.2 Comparison between the percentages of all generic medicine items claimed the percentage of generic analgesic medicine items and the percentage of generic combination analgesic medicine items claimed for the different study periods.

The percentage innovator combination analgesic medicine items prescribed steadily decreased from 2001 to 2006 while the percentage generic combination analgesic medicine items prescribed steadily increased (*See* Figure 5.3). In 2006, the percentage number of generic combination analgesics increased drastically, probably because of the number of patents expiring and the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

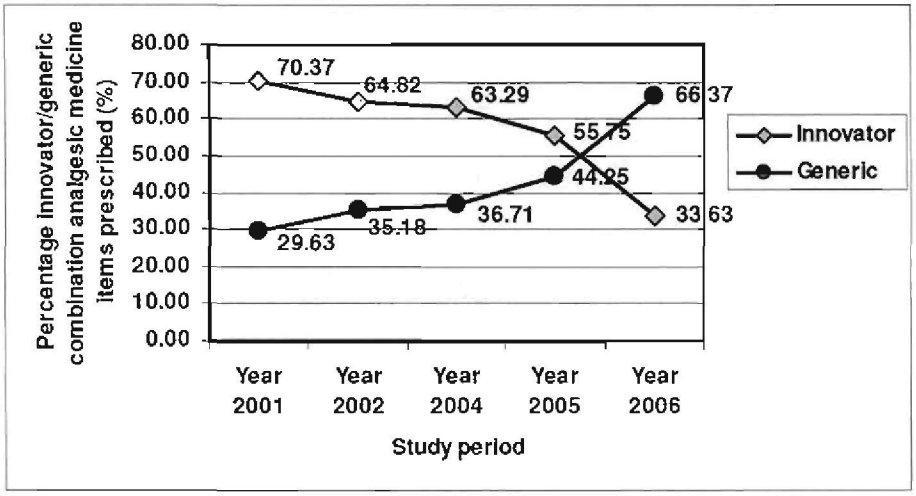

Figure 5.3 Percentage innovator and generic combination analgesic medicine items prescribed.

5.2.6 Total cost of medicine items

5.2.6.1 Total cost of medicine items claimed

The ***total cost of all medicine items*** on the ***total database*** increased with 58.37% (n=R221 641 836) from 2001 to 2002 and with 9.96% (n=R59 870 675) from 2002 to 2004. From 2004 to 2005 the total cost of all medicine items decreased with 38.62% (n=R255 391 903) and from 2005 to 2006 with 31.21% (n=R126 668 265) (refer to table 5.1).

5.2.6.2 Total cost of *analgesic* medicine items claimed by the *total database*

Analgesic medicine items represented 5.53% (n=R20 980 439.81) during 2001, 4.66% (n=R 28 022 309.02) during 2002, 3.80%(n=R 25 149 035.88) during 2004, 4.14% (n= R16 818 087.78) during 2005 and 3.81% during 2006 (n=R10 636 313.51) of the *total cost of all medicine items claimed* (N=R379 708 489.00 for 2001, N=R601 350 325.00 for 2002, N=R661 221 000.00 for 2004, N=R405 829 097.00 for 2005 and N=R279 160 832.00 for 2006) (refer to table 5.1).

The fluctuation in the cost percentage of analgesic medicine items may be due to an increased generic availability, the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30), which lead to increased generic medicine item prescribing which is less expensive, and the implementation of the new pricing regulations during May 2004 (Tshabalala-Msimang, 2004:5).

The ***total cost*** of ***analgesic items*** increased with 33.56% (n=R7 041 869.21) from 2001 to 2002. From 2002 to 2004 there was a decrease of 10.25% (n=R2 873 273.14), from 2004 to 2005 there was a decrease of 33.13% (n=R8 330 948.10) and from 2005 to 2006 the total cost of analgesic items decreased with 36.76% (n=R6 181 774.27) (refer to table 5.1).

5.2.6.3 Total cost of *combination analgesic* medicine items claimed

Combination analgesic medicine items represented 4.95% (n=R18 798 202.42) during 2001, 4.10% (n=R24 654 906.68) during 2002, 3.22% (n=R21 288 560.33) during 2004, 3.52% (n=R14 265 812.95) during 2005 and 3.15% (n=R 8 791 228.57) during 2006 of the ***total cost of all medicine items*** claimed through the database (N=R379 708 489.00 for 2001, N=R601 350 325.00 for 2002, N=R661 221 000.00 for 2004, N=R405 829 097.00 for 2005 and N=R279 160 832.00 for 2006) (refer to table 5.1).

Combination analgesic medicine items represented 89.60% (n=R18 798 202.42) during 2001, 87.98% (n=R24 654 906.68) during 2002, 84.65% (n=R21 288 560.33) during 2004, 84.82% (n=R14 265 812.95) during 2005 and 82.65% (n=R 8 791 228.57) during 2006 of the ***total cost of all analgesic medicine items*** claimed (N=R20 980 439.81 for 2001, N=R28 022 309.02 for 2002, N=R25 149 035.88 for 2004, N=R16 818 087.78 for 2005 and N=R 10 636 313.51 for 2006) (refer to table 5.1).

The decrease in the cost percentage of combination analgesic medicine items from 2001 to 2006 may be due to the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30), which lead to increased generic medicine item prescribing and availability, and the implementation of the new pricing regulations during May 2004 (Tshabalala-Msimang, 2004:5). Generic medicine items are most of the time less expensive than innovator medicine items. Therefore, the increased prescribing of less expensive items may be the cause of a general reduction in medicine prices.

The *total cost* of combination analgesic items increased with 31.16% (n=R5 856 704.26) from 2001 to 2002. From 2002 to 2004 there was a decrease of 13.65% (n=R3 366 346.35) and from 2004 to 2005 the total cost of combination analgesic items decreased with 32.99% (n=R7 022 747.38) and from 2005 to 2006 a decrease of 38.38% (n=R5 474 584.38) was seen (refer to table 5.1).

5.3 Analysis of the sub-pharmacological group: combination analgesics

The analysis of combination analgesic medicine items will be outlined in this section.

5.3.1 Prescribing patterns of generic and innovator combination analgesic medicine items

Table 5.6 provides an overview of the prescribing patterns of innovator and generic combination analgesic medicine items for the study years 2001, 2002, 2004, 2005 and 2006.

Table 5.6 Summary of the prescribing patterns of innovator and generic combination analgesic medicine items prescribing for 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Number of combination analgesic items	Prevalence of combination analgesic items (%*)	Average cost per combination analgesic item (R)	Total cost of combination analgesic items(R)	Cost of combination analgesic items (%**)	CPI
2001	Innovator	184299	70.37	86.54 ± 65.97	15949494.20	84.85	1.21
	Generic	77608	29.63	36.71 ± 27.43	2848708.22	15.15	0.51
2002	Innovator	206124	64.82	94.96 ± 74.14	19572876.29	79.39	1.22
	Generic	111873	35.18	45.43 ± 33.58	5082030.39	20.61	0.59
2004	Innovator	241664	63.29	69.78 ± 57.80	16862405.09	79.21	1.25
	Generic	140145	36.71	31.58 ± 24.72	4426155.24	20.79	0.57
2005	Innovator	156995	55.75	64.42 ± 50.93	10111090.26	70.88	1.27
	Generic	124635	44.25	33.34 ± 22.90	4154722.69	29.12	0.66
2006	Innovator	63145	33.63	63.78 ± 61.39	4027734.10	45.82	1.36
	Generic	124598	66.37	39.23 ± 26.65	4763479.17	54.18	0.82

%* Total number of innovator or generic combination analgesic medicine items divided by the corresponding total number of combination analgesic medicine items claimed during that specific period multiplied by hundred.

%** Total cost of innovator or generic combination analgesic medicine items divided by the corresponding total cost of combination analgesic medicine items claimed during that specific period multiplied by hundred

5.3.1.1 Prevalence of innovator/generic combination analgesic medicine items prescribed

Refer to section 5.2.5.3.

5.3.1.2 Average cost per innovator/generic medicine item

According to Table 5.6 the ***average cost per innovator combination analgesic medicine item*** increased from 2001 to 2002, after which a decreasing trend was seen from 2004 to 2006. The ***average cost of generic combination analgesic medicine items*** increased from 2001 to 2002, decreased from 2002 to 2004, after which an increasing trend was seen from 2004 to 2006. The changes in average cost per innovator or generic combination analgesic medicine item is possibly the result of the new pricing regulations implemented in May 2004 (Tshabalala-Msimang, 2004:5) and the increased availability of generic medicine items (South Africa, 2003:MAE30).

The effect sizes (d-values) calculated between the average cost per ***innovator and generic combination analgesic medicine items*** for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005, 2005 to 2006 and 2001 to 2006 were of no practical significance (d<0.8) (refer to section 4.7.4.5).

5.3.1.3 Total cost of innovator/ generic medicine items

The total ***cost of innovator combination analgesic medicine items*** represented 84.85% (n=R15 949 494.20) during 2001, 79.39% (n=R19 572 876.29) during 2002, 79.21% (n=R16 862 405.09) during 2004, 70.88% (n=R 10 111 090.26) during 2005 and 45.82% (n=R 4 027 734.10) during 2006 of the total cost of all combination analgesic medicine items for the corresponding year (N=R18 798 202.42 for 2001, N=R24 654 906.68 for 2002, N=R21 288 560.33 for 2004, N=R 14 265 812.95 for 2005 and N=R8 791 228.57 for 2006). The cost percentage decrease corresponds with the decrease in the prevalence of innovator combination analgesics from 2001 to 2006 (refer to Table 5.6).

The total ***cost of generic combination analgesic medicine items*** represented 15.15% (n=R2 848 708.22) during 2001, 20.61% (n=R5 082 030.39) during 2002, 20.79% (n=R4 426 155.24) during 2004, 29.12% (n=R4 154 722.69) during 2005 and 54.18% (n=R 4 763 479.17) during 2006 of the total cost of all combination analgesic medicine items for the corresponding year (N=R18 798 202.42 for 2001, N=R24 654 906.68 for 2002, N=R21 288 560.33 for 2004, N=R 14 265 812.95 for 2005 and N=R8 791 228.57 for 2006) (refer to Table 5.6). The cost percentage increase corresponds with the increase in generic prevalence percentage due to the

implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The ***total cost of innovator combination analgesic medicine items*** increased with 22.72% (n=R3 623 382.09) from 2001 to 2002, followed with a decrease of 13.85% (n=R2 710 471.20) from 2002 to 2004. From 2004 to 2005 the cost per innovator combination analgesic medicine item decreased with a further 40.04% (n=R6 751 314.83) and from 2005 to 2006 with 60.16% (n=R6 083 356.16) (refer to table 5.6).

The ***total cost of generic combination analgesic medicine items*** increased with 78.40% (n=R2 233 322.17) from 2001 to 2002, followed with a decrease of 12.91% (n=R655 875.15) from 2002 to 2004. From 2004 to 2005 the cost per generic combination analgesic medicine item decreased with a further 6.13% (n=R271 432.55) after which the cost increased with 14.65% (n=R608 756.48) (refer to table 5.6).

5.3.1.4 Cost-prevalence index of innovator/ generic medicine items

The ***cost-prevalence index*** of the ***innovator combination analgesic medicine items*** was higher than one for the whole study period (2001, 2002, 2004, 2005 and 2006), indicating that the items were relatively expensive. The ***cost-prevalence index*** of the ***generic combination analgesic medicine items*** was lower than one for the whole study period (2001, 2002, 2004, 2005 and 2006), indicating that the treatment is relatively inexpensive (refer to table 5.6).

5.3.2 Prevalence and cost of combination analgesic medicine items based on the active ingredient classification

Table 5.7, 5.8, 5.9, 5.10 and 5.11 summarises the prevalence and cost of combination analgesic medicine items based on the active ingredient classification, the prevalence percentage and cost percentage for the different combinations, the cost-prevalence index calculated for the different active ingredient combinations, the average cost per active ingredient combination, as well as the standard deviation per combination.

Table 5.7 Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2001.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Aspirin 150mg/Codeine phosphate 4mg	Innovator	39	32.80 ± 5.05	1279.36	0.01	0.01	0.68
	Aspirin 500mg/Codeine phosphate 8mg	Innovator	911	39.80 ± 19.28	36258.68	0.35	0.19	0.55
	Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	Innovator	402	151.60 ± 104.25	60942.22	0.15	0.32	**2.16**
	Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Generic	1098	68.16 ± 7.39	74837.61	0.42	0.40	0.95
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Innovator	120	73.28 ± 60.09	8794.07	0.05	0.05	0.94
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	966	88.03 ± 54.71	85040.83	0.37	0.45	**1.22**
	Aspirin/Paracetamol/Caffeine	Generic	19	3.09 ± 1.25	58.65	0.01	0.00	0.03
	Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg	Innovator	177	41.40 ± 25.79	7328.08	0.07	0.04	0.56
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Innovator	8849	183.78 ± 113.60	1626255.91	3.38	8.65	**2.56**
	Ibuprofen 200mg/ Paracetamol 250mg	Innovator	24867	57.84 ± 20.40	1438389.69	9.49	7.65	0.81
	Ibuprofen 400mg/ Paracetamol 325mg	Innovator	545	66.42 ± 24.75	36198.93	0.21	0.19	0.92
	Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg	Innovator	74483	85.78 ± 38.20	6389053.43	28.72	33.99	**1.18**
	Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg	Generic	14601	66.92 ± 21.62	977076.80	6.04	5.20	0.86

Table 5.7 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2001.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence%	Cost %@	CPI
2001	Orphenadrine citr. 35mg/ Paracetamol 450mg	Innovator	4818	37.14 ± 18.50	178922.93	1.84	0.95	0.52
		Generic	853	38.07 ± 1.25	32470.44	0.33	0.17	0.52
	Paracetamol 100mg/ Aspirin 400mg/ Caffeine anhydrous 30mg	Innovator	3	14.20 ± 6.35	42.59	0.00	0.00	0.00
	Paracetamol 500mg/Chlormezanone 100mg	Innovator	1	37.67 ± 0.00	37.67	0.00	0.00	0.00
		Generic	7	20.51 ± 7.71	143.58	0.00	0.00	0.00
	Paracetamol 120mg/ Codeine phosphate 5mg	Innovator	37	23.16 ± 7.45	856.87	0.01	0.00	0.46
	Paracetamol 320mg/ Codeine phosphate 8mg	Innovator	245	27.14 ± 16.15	6649.00	0.10	0.04	0.35
		Generic	63	34.20 ± 9.31	2154.31	0.02	0.01	0.57
	Paracetamol 500mg/ Codeine phosphate 10mg	Innovator	2269	17.76 ± 8.96	40293.31	0.87	0.21	0.25
		Generic	3	25.77 ± 5.14	77.32	0.00	0.00	0.00
	Paracetamol 500mg/ Codeine phosphate 20mg	Innovator	1501	46.60 ± 17.99	69950.25	0.57	0.37	0.65
	Paracetamol 500mg/ Codeine phosphate 8mg	Innovator	130	58.53 ± 35.14	7609.46	0.05	0.04	0.81
		Generic	3194	28.24 ± 18.76	90206.37	1.22	0.48	0.39
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Innovator	349	51.03 ± 33.68	17807.93	0.13	0.09	0.73
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	8228	103.75 ± 65.27	853692.18	3.14	4.54	**1.45**
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Innovator	8505	71.54 ± 50.47	608476.71	3.25	3.24	**1.00**
		Generic	34383	20.28 ± 14.32	697245.43	13.13	3.71	0.28
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	2800	56.68 ± 37.50	158694.32	1.07	0.84	0.79
		Generic	1316	45.35 ± 24.35	59684.89	0.50	0.32	0.64

Table 5.7 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2001.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Innovator	5241	70.33 ± 41.00	368592.67	2.00	1.96	0.98
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Innovator	2591	50.00 ± 18.49	129555.93	0.99	0.69	0.70
	Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg	Innovator	9274	34.97 ± 13.72	324283.79	3.54	1.73	0.49
		Generic	10344	31.06 ± 10.53	321297.57	3.94	1.71	0.43
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	13058	165.27 ± 96.79	2158054.66	5.29	11.48	**2.17**
	Paracetamol 120mg/ Doxylamine succinate 5mg	Innovator	214	34.68 ± 6.68	7420.81	0.08	0.04	0.49
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	Innovator	4199	59.56 ± 41.61	249998.77	1.60	1.33	0.83
		Generic	11310	50.43 ± 35.30	570396.94	4.31	3.03	0.70
	Paracetamol 500mg/ Mephenesin 150mg	Innovator	1217	43.90 ± 22.58	53425.66	0.46	0.28	0.62
	Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg	Innovator	861	45.63 ± 40.34	39287.10	0.33	0.21	0.63
		Generic	207	66.67 ± 23.84	13801.62	0.08	0.07	0.92
	Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg	Innovator	1621	56.73 ± 33.24	91960.62	0.62	0.49	0.79
		Generic	199	43.77 ± 31.01	8709.93	0.07	0.05	0.66
	Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg	Innovator	177	25.24 ± 15.58	4466.92	0.07	0.02	0.34
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Innovator	1371	202.37 ± 141.56	277448.44	0.52	1.48	**2.84**

Table 5.7 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2001.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Innovator	1200	115.14 ± 58.88	138165.83	0.46	0.73	**1.60**
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Innovator	3041	156.13 ± 89.75	474805.34	1.16	2.53	**2.18**
	TOTAL		**261907**	**71.77 ± 61.67**	**18798202.42**	**101.02**	**100.00**	

Table 5.8 Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2002.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2002	Aspirin/Caffeine	Innovator	1	22.99 ± 0.00	22.99	0.00	0.00	0.00
	Aspirin 150mg/Codeine phosphate 4mg	Innovator	8	36.11 ± 10.88	288.86	0.00	0.00	0.47
	Aspirin 500mg/Codeine phosphate 8mg	Innovator	1097	43.48 ± 20.39	47692.62	0.34	0.19	0.57
	Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	Innovator	311	197.69 ± 125.72	61480.98	0.10	0.25	**2.49**
	Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Generic	561	74.77 ± 12.21	41946.91	0.18	0.17	0.95
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Innovator	158	84.24 ± 47.48	13310.55	0.05	0.05	**1.08**
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	851	108.07 ± 68.53	91969.32	0.27	0.37	**1.38**
	Aspirin/Paracetamol/Caffeine	Generic	8	4.84 ± 1.84	38.69	0.00	0.00	0.00
	Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg	Innovator	771	48.72 ± 28.48	37559.41	0.24	0.15	0.63
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Innovator	9974	201.31 ± 123.90	2007845.92	3.14	8.14	**2.59**
	Ibuprofen 200mg/ Paracetamol 250mg	Innovator	28738	66.84 ± 23.59	1920957.53	9.04	7.79	0.86
	Ibuprofen 400mg/ Paracetamol 325mg	Innovator	5448	76.65 ± 29.46	417613.43	1.71	1.69	0.99
	Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg	Innovator	80151	91.55 ± 42.60	7337687.56	25.20	29.76	**1.18**

Table 5.8 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2002.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2002	Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg	Generic	34035	76.23 ± 26.74	2594330.29	10.70	10.52	0.98
	Orphenadrine citr. 35mg/ Paracetamol 450mg	Innovator	6869	43.98 ± 19.88	302078.99	2.16	1.23	0.57
		Generic	1184	43.99 ± 19.65	52086.21	0.37	0.21	0.57
	Paracetamol 100mg/ Aspirin 400mg/ Caffeine anhydrous 30mg	Innovator	9	21.95 ± 12.86	197.58	0.00	0.00	0.00
	Paracetamol 120mg/ Codeine phosphate 5mg	Innovator	51	23.32 ± 5.42	1189.42	0.02	0.00	0.24
	Paracetamol 320mg/ Codeine phosphate 8mg	Innovator	230	28.55 ± 14.00	6565.42	0.08	0.03	0.33
		Generic	15	35.08 ± 17.57	526.22	0.00	0.00	0.00
	Paracetamol 500mg/ Codeine phosphate 10mg	Innovator	2651	19.45 ± 9.99	51558.86	0.83	0.21	0.25
		Generic	7	24.17 ± 10.65	169.21	0.00	0.00	0.00
	Paracetamol 500mg/ Codeine phosphate 20mg	Innovator	1122	52.57 ± 20.18	58986.46	0.35	0.24	0.68
	Paracetamol 500mg/ Codeine phosphate 8mg	Innovator	311	40.40 ± 29.80	12563.68	0.09	0.05	0.57
		Generic	3638	31.13 ± 20.23	113260.59	1.14	0.46	0.40
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Innovator	339	56.00 ± 37.38	18982.64	0.11	0.08	0.70
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	7024	129.64 ± 82.08	910557.07	2.21	3.69	**1.67**
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Innovator	8516	86.55 ± 61.76	737036.59	2.68	2.99	**1.12**
		Generic	41985	21.17 ± 15.11	888883.79	13.16	3.61	0.27
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	4059	63.89 ± 40.81	259313.86	1.28	1.05	0.82
		Generic	1636	53.42 ± 28.24	87395.00	0.52	0.35	0.68
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Innovator	4231	79.05 ± 46.14	334465.86	1.33	1.36	**1.02**

Table 5.8 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2002.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2002	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Innovator	3375	57.26 ± 22.62	193240.41	1.06	0.78	0.74
	Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg	Innovator	9629	37.4 ± 16.71	360816.14	3.02	1.46	0.48
		Generic	11838	32.34 ± 13.18	382857.25	3.71	1.55	0.42
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	15533	181.07 ± 107.72	2812513.87	4.88	11.41	**2.34**
	Paracetamol 120mg/ Doxylamine succinate 5mg	Innovator	183	41.09 ± 8.62	7519.55	0.06	0.03	0.51
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	Innovator	5778	67.20 ± 47.65	388263.68	1.81	1.57	0.87
		Generic	16609	54.11 ± 38.64	898664.49	5.21	3.64	0.70
	Paracetamol 500mg/ Mephenesin 150mg	Innovator	1895	50.64 ± 23.64	95960.82	0.60	0.39	0.65
	Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg	Innovator	525	77.53 ± 57.58	40702.58	0.17	0.17	0.97
		Generic	206	67.53 ± 33.87	13910.88	0.06	0.06	0.94
	Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg	Innovator	1283	75.75 ± 32.61	97188.52	0.41	0.39	0.96
		Generic	150	52.79 ± 16.24	7918.11	0.05	0.03	0.64
	Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg	Innovator	241	28.28 ± 16.60	6814.54	0.08	0.03	0.35
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Innovator	1173	252.90 ± 188.98	296649.50	0.37	1.20	**3.25**
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Innovator	393	157.76 ± 95.53	62000.21	0.12	0.25	**2.10**
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Innovator	3197	181.83 ± 133.30	581323.62	1.01	2.36	**2.33**
	TOTAL		**317997**	**78.57 ± 68.48**	**24654906.68**	**99.94**	**100.00**	

Table 5.9 Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2004.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2004	**Aspirin/Caffeine**	Innovator	14	21.51 ± 11.65	301.13	0.00	0.00	0.39
	Aspirin 500mg/Codeine phosphate 8mg	Innovator	895	37.29 ± 22.43	33378.51	0.23	0.16	0.68
	Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	Innovator	9	283.45 ± 345.49	2551.01	0.00	0.01	**5.08**
	Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Generic	195	42.50 ± 8.76	8287.19	0.05	0.04	0.78
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Innovator	167	84.72 ± 63.76	14148.14	0.04	0.07	**1.66**
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	1130	77.00 ± 57.12	87010.25	0.30	0.41	**1.36**
	Aspirin/Paracetamol/Caffeine	Generic	2	1.36 ± 0.00	2.72	0.00	0.00	0.00
	Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg	Innovator	24	28.78 ± 11.28	690.74	0.01	0.00	0.32
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Innovator	10047	159.72 ± 117.64	1604744.87	2.63	7.54	**2.87**
	Ibuprofen 200mg/ Paracetamol 250mg	Innovator	30608	54.90 ± 21.60	1680457.13	8.01	7.89	0.99
	Ibuprofen 400mg/ Paracetamol 325mg	Innovator	5911	60.94 ± 26.53	360206.74	1.55	1.69	**1.09**
	Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg	Innovator	102416	64.70 ± 28.34	6626117.34	26.82	31.13	**1.16**

Table 5.9 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2004.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2004	Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg	Generic	50018	48.71 ± 20.33	2436343.51	13.10	11.44	0.87
	Ibuprofen 200mg/Codeine phosphate 10mg	Innovator	10	39.98± 34.58	399.79	0.00	0.00	0.00
	Ibuprofen 200mg/Paracetamol 350mg	Innovator	86	29.65 ± 10.00	2550.28	0.02	0.01	0.60
	Orphenadrine citr. 35mg/ Paracetamol 450mg	Innovator	9524	37.99 ± 16.54	361788.26	2.49	1.70	0.68
		Generic	1251	33.82 ± 18.57	42303.47	0.32	0.20	0.62
	Paracetamol 100mg/ Aspirin 400mg/ Caffeine anhydrous 30mg	Innovator	177	29.12 ± 16.51	5153.40	0.05	0.02	0.48
	Paracetamol 120mg/ Codeine phosphate 5mg	Innovator	23	17.01 ± 6.18	391.15	0.01	0.00	0.18
	Paracetamol 320mg/ Codeine phosphate 8mg	Innovator	482	27.70 ± 39.60	13352.95	0.13	0.06	0.48
	Paracetamol 500mg/ Codeine phosphate 10mg	Innovator	3068	13.42 ± 9.37	41169.44	0.80	0.19	0.24
	Paracetamol 500mg/ Codeine phosphate 20mg	Innovator	719	48.07± 26.52	34565.28	0.19	0.16	0.85
	Paracetamol 500mg/ Codeine phosphate 8mg	Innovator	373	32.81 ± 14.76	12238.37	0.10	0.06	0.58
		Generic	3426	25.02 ± 17.29	85715.58	0.90	0.40	0.45
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Innovator	338	39.43 ± 28.76	13325.79	0.09	0.06	0.70
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	7515	78.33 ± 63.98	588618.34	1.97	2.76	**1.40**
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Innovator	10066	65.46 ± 57.22	658909.08	2.64	3.10	**1.17**
		Generic	48892	15.38 ± 12.53	751799.62	12.76	3.53	0.28

Table 5.9 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2004.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2004	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	3519	47.65 ± 35.55	167686.17	0.92	0.79	0.86
		Generic	1713	35.74 ± 23.98	61218.59	0.45	0.29	0.64
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Innovator	2353	65.62 ± 48.73	154415.09	0.62	0.73	**1.17**
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Innovator	2703	35.95 ± 30.94	97173.47	0.71	0.46	0.64
	Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg	Innovator	9769	26.42 ± 17.91	258085.33	2.56	1.21	0.47
		Generic	11791	18.56 ± 14.60	218883.23	3.09	1.03	0.33
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	18315	129.60 ± 86.39	2373696.43	4.80	11.15	**2.32**
	Paracetamol 120mg/ Doxylamine succinate 5mg	Innovator	1	30.21 ± 0.00	30.21	0.00	0.00	0.00
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	Innovator	5006	49.56 ± 43.36	248078.29	1.31	1.17	0.89
		Generic	22668	35.97 ± 31.65	815351.12	5.92	3.83	0.65
	Paracetamol 500mg/ Mephenesin 150mg	Innovator	2987	33.10 ± 17.82	98883.21	0.78	0.46	0.60
	Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg	Innovator	509	58.82 ± 34.80	29940.79	0.13	0.14	**1.08**
		Generic	88	35.16 ± 28.02	3094.03	0.02	0.01	0.73
	Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg	Innovator	446	69.05 ± 30.04	30794.50	0.11	0.14	**1.32**
		Generic	5	41.22 ± 34.85	206.11	0.00	0.00	0.00

Table 5.9 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2004.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2004	**Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg**	Innovator	520	19.95 ± 11.56	10372.39	0.14	0.05	0.35
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Innovator	944	153.72 ± 114.24	145112.83	0.25	0.68	**2.73**
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Innovator	557	93.45 ± 65.15	52050.90	0.15	0.24	**1.63**
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Innovator	3740	153.79 ± 121.61	575156.80	0.98	2.70	**2.76**
	Paracetamol 325mg/Tramadol HCL 37.5mg	Innovator	6789	70.97 ± 47.02	481810.76	1.78	2.26	**1.27**
	TOTAL		**381809**	**55.80 ± 51.76**	**21288560.33**	**99.96**	**100.00**	

Table 5.10 Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2005.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2005	**Aspirin/Caffeine**	Innovator	2	30.81 ± 30.79	61.62	0.00	0.00	0.61
	Aspirin 500mg/Codeine phosphate 8mg	Innovator	575	33.90 ± 20.82	19495.22	0.20	0.14	0.68
	Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	Innovator	1	111.80 ± 0.00	111.80	0.00	0.00	**2.21**
	Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Generic	61	33.83 ± 10.40	2063.39	0.02	0.01	0.72
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Innovator	126	65.06 ± 80.88	8197.93	0.04	0.06	**1.44**
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	1124	64.21 ± 40.16	72170.60	0.40	0.51	**1.27**
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Innovator	6285	154.16 ± 107.52	968906.27	2.23	6.79	**3.05**
	Ibuprofen 200mg/ Paracetamol 250mg	Innovator	3306	11.10 ± 19.24	36683.75	1.17	0.26	0.22
		Generic	21115	49.46 ± 19.20	1044324.05	7.49	7.32	0.98
	Ibuprofen 400mg/ Paracetamol 325mg	Innovator	4290	57.60 ± 22.05	247095.32	1.52	1.73	**1.14**
	Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg	Innovator	66673	66.24 ± 28.56	4416592.27	23.68	30.96	**1.31**
		Generic	19299	45.08 ± 16.04	869910.06	6.85	6.10	0.89
	Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg	Generic	43940	48.39 ± 19.26	2126139.99	15.63	14.90	0.96
	Ibuprofen 200mg/Codeine phosphate 10mg	Innovator	542	32.13 ± 11.16	17416.91	0.19	0.12	0.64
	Ibuprofen 200mg/Paracetamol 350mg	Innovator	1961	35.33 ± 14.54	69286.59	0.70	0.49	0.69

Table 5.10 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2005.

	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2005	Orphenadrine citr. 35mg/ Paracetamol 450mg	Innovator	9551	34.33 ± 14.96	327883.80	3.39	2.30	0.68
		Generic	679	27.90 ± 16.06	18944.28	0.24	0.13	0.55
	Paracetamol 100mg/ Aspirin 400mg/ Caffeine anhydrous 30mg	Innovator	36	25.85 ± 14.71	930.58	0.01	0.01	0.65
	Paracetamol 120mg/ Codeine phosphate 5mg	Innovator	2	19.30 ± 11.70	38.59	0.00	0.00	0.00
	Paracetamol 320mg/ Codeine phosphate 8mg	Innovator	256	19.15 ± 36.09	4901.15	0.09	0.03	0.38
	Paracetamol 500mg/ Codeine phosphate 10mg	Innovator	1663	10.62 ± 12.63	17657.70	0.59	0.12	0.21
	Paracetamol 500mg/ Codeine phosphate 20mg	Innovator	323	49.58 ± 28.87	16013.71	0.11	0.11	**1.02**
	Paracetamol 500mg/ Codeine phosphate 8mg	Innovator	112	24.97 ± 10.31	2796.99	0.03	0.02	0.65
		Generic	2042	24.30 ± 16.83	49614.97	0.73	0.35	0.48
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Innovator	177	26.85 ± 14.67	4751.62	0.06	0.03	0.56
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	6214	63.87 ± 42.56	396911.31	2.21	2.78	**1.26**
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Innovator	6778	42.32 ± 42.79	286854.62	2.40	2.01	0.84
		Generic	29049	14.12 ± 10.74	410295.68	10.24	2.88	0.28
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	500	39.57 ± 35.36	19783.25	0.18	0.14	0.77
		Generic	766	29.90 ± 21.08	22903.54	0.28	0.16	0.57
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Innovator	820	87.47 ± 99.51	71726.03	0.29	0.50	**1.73**

Table 5.10 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2005.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2005	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Innovator	347	9.56 ± 4.15	3318.80	0.12	0.02	0.19
	Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg	Innovator	6496	18.44 ± 13.30	119786.67	2.31	0.84	0.36
		Generic	7136	13.30 ± 6.91	94902.61	2.53	0.67	0.26
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	10788	116.00 ± 69.69	1251424.30	3.83	8.77	**2.29**
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	Innovator	2604	29.43 ± 27.38	76645.03	0.92	0.54	0.58
		Generic	15832	27.55 ± 23.84	436133.15	5.61	3.06	0.54
	Paracetamol 500mg/ Mephenesin 150mg	Innovator	1445	24.35 ± 13.14	35187.00	0.51	0.25	0.48
	Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg	Innovator	79	62.46 ± 44.70	4934.46	0.03	0.03	**1.15**
		Generic	22	19.44 ± 11.32	427.77	0.01	0.00	0.30
	Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg	Innovator	137	59.11 ± 21.09	8097.47	0.05	0.06	**1.14**
	Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg	Innovator	449	14.94 ± 6.27	6706.43	0.16	0.05	0.29
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Innovator	472	158.79 ± 116.06	74950.41	0.17	0.53	**3.09**
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Innovator	341	69.97 ± 30.10	23861.46	0.12	0.17	**1.39**
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Innovator	1382	139.11 ± 104.57	192248.80	0.49	1.35	**2.75**
	Paracetamol 325mg/Tramadol HCL 37.5mg	Innovator	5792	66.77 ± 54.42	386725.00	2.06	2.71	1.32
	TOTAL		**281590**	**50.73 ± 43.78**	**14265812.95**	**99.89**	**100.0**	

Table 5.11 Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2006.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2006	Aspirin 500mg/Codeine phosphate 8mg	Innovator	196	37.58±17.29	7366.44	0.10	0.08	0.80
	Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Generic	17	25.66±12.00	436.17	0.01	0.00	0.50
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Innovator	9	57.43±54.20	516.88	0.01	0.01	0.59
	Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	332	84.92±85.28	28193.45	0.18	0.32	**1.78**
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Innovator	3642	175.21±110.21	638117.69	1.94	7.26	**3.74**
	Ibuprofen 200mg/ Paracetamol 250mg	Innovator	5836	46.74±19.73	272766.35	3.11	3.10	**1.00**
		Generic	13634	14.18±22.07	193336.15	7.26	2.20	0.30
	Ibuprofen 400mg/ Paracetamol 325mg	Innovator	2783	63.08±22.97	175539.69	1.48	2.00	**1.35**
	Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg	Innovator	17449	54.17±20.90	945149.66	9.29	10.75	**1.16**
		Generic	44651	45.38±15.15	2026263.21	23.79	23.05	0.97
	Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg	Generic	32002	54.63±31.24	1748334.19	17.04	19.89	**1.17**
	Ibuprofen 200mg/Codeine phosphate 10mg	Innovator	377	38.57±11.88	14539.87	0.20	0.17	0.83
	Ibuprofen 200mg/Paracetamol 350mg	Innovator	1061	35.95±	38141.30	0.57	0.43	0.76
	Orphenadrine citr. 35mg/ Paracetamol 450mg	Innovator	7720	34.98±13.35	270011.55	4.11	3.07	0.75
		Generic	577	23.21±18.39	13393.55	0.30	0.15	0.51
	Paracetamol 320mg/ Codeine phosphate 8mg	Innovator	59	13.86±7.82	817.98	0.03	0.01	0.31

Table 5.11 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2006	Paracetamol 500mg/ Codeine phosphate 10mg	Innovator	1131	11.97±4.01	13538.67	0.60	0.15	0.26
	Paracetamol 500mg/ Codeine phosphate 20mg	Innovator	176	57.24±27.11	10073.68	0.09	0.11	**1.27**
	Paracetamol 500mg/ Codeine phosphate 8mg	Innovator	45	22.53±10.73	1013.96	0.02	0.01	0.58
		Generic	753	24.39±15.71	18362.04	0.40	0.21	0.52
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Innovator	102	35.36±23.02	3607.21	0.05	0.04	0.82
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Innovator	2155	69.89±50.72	150609.46	1.15	1.71	**1.49**
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Innovator	3456	57.29±50.56	197978.95	1.84	2.25	**1.22**
		Generic	14307	16.19±10.64	231559.58	7.61	2.63	0.35
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	151	35.18±38.23	5312.63	0.08	0.06	0.76
		Generic	416	44.70±26.45	18595.33	0.22	0.21	0.96
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Innovator	777	98.14±59.24	76256.65	0.42	0.87	**2.07**
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Innovator	62	10.61±6.36	657.82	0.03	0.01	0.25
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Innovator	3282	16.68±10.48	54754.58	1.75	0.62	0.36
		Generic	4101	14.16±5.50	58077.50	2.18	0.66	0.30
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Innovator	3752	132.48±84.25	497056.37	2.00	5.65	**2.83**

Table 5.11 (continue) Prevalence, cost and cost-prevalence index values of combination analgesic medicine items based on the active ingredient combination classification for the year 2006.

Period	Active ingredient combination	Innovator/ Generic	Prevalence	Average cost (R)	Total cost (R)	Prevalence%*	Cost %@	CPI
2006	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	Innovator	2308	31.28±25.49	72201.86	1.23	0.82	0.67
		Generic	12699	31.69±26.25	402374.69	6.76	4.58	0.68
	Paracetamol 500mg/ Mephenesin 150mg	Innovator	669	26.97±18.58	18043.63	0.36	0.21	0.57
	Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 30mg/ Meprobamate 200mg	Innovator	6	28.79±14.21	172.76	0.00	0.00	0.00
		Generic	5	16.18±6.26	80.89	0.00	0.00	0.00
	Paracetamol 450mg/ Codeine phosphate 10mg/ Caffeine 50mg	Innovator	33	52.08±20.21	1718.48	0.02	0.02	0.98
	Paracetamol 500mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 125mg	Innovator	120	17.63±8.97	2116.15	0.06	0.02	0.40
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Innovator	367	159.81±103.43	58651.57	0.20	0.67	**3.34**
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Innovator	128	81.16±50.90	10388.89	0.07	0.12	**1.69**
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Innovator	318	148.13±109.06	47106.65	0.17	0.54	**3.15**
	Paracetamol 325mg/Tramadol HCL 37.5mg	Innovator	6081	76.96±68.96	467994.44	3.24	5.32	**1.64**
	TOTAL		187745	46.83±43.41	8791228.57	99.97	100.00	

As shown in table 5.7, 5.8, 5.9, 5.10 and 5.11, the combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg represented the active ingredient combination with the ***highest prevalence*** for the entire study period, being 74483 (28.44%; N=261907) for 2001, 80151 (25.20%; N=317997) for 2002, 102416 (26.82%; N=381809) for 2004, 85792 (30.53%; N=281590) for 2005 and 62 100 (33.08%; n=187 745) for 2006. This combination also represented the active ingredient combination with the ***highest total cost*** for the entire study period, being R6 389 053.43 (33.99%; N=R 18 798 202.42) for 2001, R7 337 687.66 (29.76%; N=R24 654 906.68) for 2002, R6626117.34 (31.13%; N=R21 288 560.33) for 2004, R5 286 502.33 (37.06%; N=R14 265 812.95) for 2005 and R 2971412.87 (33.80%; N=R 8 91 228.57) for 2006. The combination has a cost-prevalence index > 1 for the entire study period, indicating that it is relatively expensive.

During 2001, the combination of paracetamol 500mg and chlormezanone 100mg and the combination of paracetamol 100mg, aspirin 400mg and caffeine anhydrous 30mg represented the combinations with the ***lowest prevalence*** of respectively 8 (0.00%; N=261907) and 3 (0.00%; N=261907). These two combinations also represent the ***lowest total costs*** of respectively R181.25 (0.00%; N=R 18 798 202.42) and R42.59 (0.00%; N=R18 798 202.42) during the same year. The combination of paracetamol 120mg an codeine phosphate 5mg also represent the lowest total cost of R856.87 (0.00%; N=R 18 798 202.42) during 2001 (Refer to table 5.7).

During 2002, the combination of aspirin and caffeine, the combination of aspirin 150mg and codeine phosphate 8mg, the combination of aspirin, paracetamol and caffeine and the combination of paracetamol 100mg, aspirin 400mg and caffeine anhydrous 30mg represented the combinations with the ***lowest prevalence*** of respectively 1 (0.00%; N=317997), 8 (0.00%; N=317997), 8 (0.00%; N=317997) and 9 (0.00%; N=317997). During the same year these four combinations also represented the ***lowest total costs*** of respectively R22.99 (0.00%; N=R24 654 906.68), R288.86 (0.00%; N=R24 654 906.68), R38.69 (0.00%; N= R24 654 906.68) and R197.58 (0.00%; N=R24 654 906.68). The combination of paracetamol 120mg an codeine phosphate 5mg also represented the lowest total cost of R1189.42 (0.00%;N=R24 654 906.68) during 2002 (Refer to table 5.8).

The combination of aspirin and caffeine, the combination of aspirin 200mg, *paracetamol 200mg, chlorphenoxamine HCL 2mg, codeine phosphate 15mg,* caffeine 50mg and phenobarbitone 5mg, the combination of aspirin, paracetamol and caffeine, the combination of ibuprofen 200mg and codeine phosphate 10mg, combination of paracetamol 12mg and doxylamine succinate 5mg and the generic of the combination of paracetamol 450mg, codeine phosphate 10mg and caffeine 50mg represented the combinations with the ***lowest prevalence*** of respectively 14 (0.00%;N=381809), 9

(0.00%;N=381809), 2 (0.00%;N=381809), 10 (0.00%;N=381809), 1 (0.00%;N=381809) and 5 (0.00%;N=381809) during 2004. The combination of aspirin and caffeine, the combination of aspirin, paracetamol and caffeine, the combination of dextropropoxyphene HCl 65mg, paracetamol 400mg and caffeine 30mg, the combination of ibuprofen 200mg and codeine phosphate 10mg, the combination of paracetamol 120mg and codeine phosphate 5mg, the combination of paracetamol 12mg and doxylamine succinate 5mg and the generic of the combination of paracetamol 45mg, codeine phosphate 10mg and caffeine 50mg represented the combinations with the ***lowest total cost*** of respectively R301.13 (0.00%;N=R21 288 560.33), R2.72 (0.00%;N= R 21 288 560.33), R690.74 (0.00%;N=R 21 288 560.33), R399.79 (0.00%;N=R21 288 560.33), R391.15 (0.00%;N=R21 288 560.33), R30.21 5 (0.00%;N= R21 288 560.33) and R34.85 (0.00%;N=R21 288 560.33) during 2004 (refer to table 5.9).

During 2005, the combination of aspirin and caffeine, the combination of aspirin 200mg, paracetamol 200mg, chlorphenoxamine HCL 2mg, codeine phosphate 15mg, caffeine 50mg and phenobarbitone 5mg and the combination of paracetamol 120mg and codeine phosphate 5mg represented the combinations with the ***lowest prevalence*** of respectively 2 (0.00%; N=281590), 1 (0.00%; N=281590) and 2 (0.00%; N=281590). These three combinations also represent the ***lowest total costs*** of respectively R61.62 (0.00%; N=R14 265 812.95), R111.80 (0.00%; N=R14 265 812.95) and R38.59 (0.00%; N=R14 265 812.95) during 2005 (Refer to table 5.10).

The combination of paracetamol 400mg, codeine phosphate 8mg, caffeine 30mg and meprobamate 200mg represented the combination with the ***lowest prevalence*** of respectively 6 (0.00%; N=187 745) innovators and 5 (0.00%; N=187 745) generics during 2006 (Refer to table 5.11). This combination also represent the ***lowest total costs*** of respectively R172.76 (0.00%; N=R8 91 228.57) for the innovators and R80.89 (0.00%; N=R8 91 228.57) for the generics. The combination of aspirin 37.5mg, paracetamol 325mg and codeine phosphate also represented the lowest total cost of R436.17 (0.00%; N=R8 91 228.57) (Refer to table 5.11).

In the years 2001, 2002, 2005 and 2006 the combination of propoxyphene HCl 65mg, aspirin 375mg and caffeine 30mg represented the ***highest average cost*** of R202.37 ± 141.56, R252.90 ± R188.98, R158.79 ± 116.06 and R159.81 ± 103.43 respectively. The combination of aspirin 200mg, paracetamol 200mg, chlorphenoxamine HCL 2mg, codeine phosphate 15mg, caffeine 50mg and phenobarbitone 5mg represented the ***highest average cost*** of R283.45 ± 345.49 for 2004.

For the years 2001, 2002 and 2004 the generic of the aspirin, paracetamol, and caffeine combination had the ***lowest average cost*** of R3.09 ± 1.25, R4.84 ± 1.84 and R1.36 ± 0.00 respectively. The combination of paracetamol

400mg, codeine phosphate 8mg, phenyltoloxamine citrate 12mg and caffeine 32mg had the ***lowest average cost*** for 2005 and 2006 of R9.56 ± 4.15 and R10.61 ± 6.36 respectively (Refer to tables 5.7 to 5.11).

The ***cost-prevalence indexes*** of the following ***innovator combinations*** were ***higher than one*** during the entire study period, indicating that these combinations were all relatively expensive (Refer to Tables 5.7 to 5.11).

- Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg
- Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg
- Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg
- Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg
- Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg
- Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg
- Propoxyphene HCl 50mg/ Paracetamol 325mg
- Propoxyphene HCl 65mg/ Paracetamol 250mg

The ***cost-prevalence indexes*** of the following ***innovator combinations*** were ***higher than one*** for certain study years, indicating that these combinations were relatively expensive.

- Aspirin 200mg/ Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg (2001-2002 and 2004-2005).
- Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 32mg/ Meprobamate 150mg (2001, 2002 and 2006).
- Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg (2002, 2004 and 2005).
- Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg (2002 and 2004-2006).
- Ibuprofen 400mg/ Paracetamol 325mg (2004-2006).
- Paracetamol 450mg/ codeine phosphate 10mg/ caffeine 50mg (2004-2005).
- Paracetamol 325mg/ Tramadol 37.5mg (2004-2006).
- Paracetamol 500mg/ Codeine phosphate 20mg (2005-2006).
- Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg (2006).

5.3.3 Individual combination analgesic medicine items

The utilisation patterns and the costs of individual combination analgesic medicine items will be discussed in this section.

5.3.3.1 Aspirin 150mg/ codeine phosphate 4mg

According to the database, there was only one aspirin 150mg and codeine phosphate 4mg innovator combination analgesic product, Dostil® Paediatric Syrup, claimed. The cost and prevalence of the aspirin 150mg and codeine phosphate 4mg analgesic combination are described in Table 5.12.

Table 5.12 Prevalence and cost of individual medicine items containing Aspirin 150mg and Codeine phosphate 4mg for the period 2001 and 2002.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Dostil®Paed Syr (S2)	39	32.80 ± 5.05	1279.36	0.01	0.01	0.68
2002	Innovator	Dostil®Paed Syr (S2)	8	36.11 ± 10.88	288.86	0.00	0.00	0.47

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Dostil® Paediatric Syrup decreased from 39 to 8 from 2001 of 2002 representing a very low percentage usage of 0.01% and 0.00% respectively for 2001 and 2002. Furthermore, the CPI is <1 for both years, giving us an indication of low usage and low cost.

The average cost of Dostil® Paediatric Syrup increase from 2001 to 2002. The effect sizes (d-values) calculated between the average cost per medicine item for Dostil® Paediatric Syrup for the periods 2001 to 2002 is of no practical significance (d<0.8).

Dostil®Paediatric Syrup was discontinued before 2004; this can be a result of the low usage of this medicine product.

5.3.3.2 Aspirin/ Caffeine

According to the database, there was only one aspirin and caffeine innovator combination analgesic product, Anadin® Regular, claimed. The cost and prevalence of the aspirin and caffeine analgesic combination is described in Table 5.13.

Table 5.13 Prevalence and cost of individual medicine items containing Aspirin and Caffeine for the period 2002, 2004 and 2005.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2002	Innovator	Anadin® Regular (S2)	1	22.99 ± 0.00	22.99	0.00	0.00	0.30
2004	Innovator	Anadin® Regular (S2)	14	21.51 ± 11.65	301.13	0.00	0.00	0.39
2005	Innovator	Anadin® Regular (S2)	2	30.81 ± 30.79	61.62	0.00	0.00	0.61

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The product has a very low percentage usage of 0.00% for the period 2002 to 2005. Furthermore, the CPI is <1 for all three years, giving us an indication of low usage and low cost.

The average cost decreased from 2002 to 2004, and increased from 2004 to 2005. The effect sizes (d-values) calculated between the average cost per medicine item for Anadin® Regular for the periods 2002 to 2004 and 2004 to 2005 were of no practical significance (d<0.8).

Anadin® Regular was not prescribed during 2006, probably because of the low utilisation.

5.3.3.3 Aspirin 150mg/ Codeine phosphate 8mg

According to the database, there was only one aspirin 150mg and codeine phosphate 8mg innovator combination analgesic product, Codis® Tablets, claimed until 2006. In 2006 Disprin Plus® tablets were also introduced. The cost and prevalence of the aspirin 150mg and codeine phosphate 8mg analgesic combination is described in Table 5.14.

Table 5.14 Prevalence and cost of individual medicine items containing Aspirin 150mg and Codeine phosphate 8mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Codis® Tab (S2)	911	39.80 ± 19.28	36258.68	0.35	0.19	0.55
2002	Innovator	Codis® Tab (S2)	1097	43.48 ± 20.39	47692.62	0.34	0.19	0.57
2004	Innovator	Codis® Tab (S2)	895	37.29 ± 22.43	33378.51	0.23	0.16	0.68
2005	Innovator	Codis® Tab (S2)	575	33.90 ± 20.82	19495.22	0.20	0.14	0.68
2006	Innovator	Codis® Tab (S2)	150	37.83±17.71	5674.32	0.08	0.06	0.81
	Innovator	Disprin Plus® Tab (S2)	46	36.79±15.98	1692.12	0.02	0.02	0.79

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The total number of medicine items containing aspirin 150mg and Codeine phosphate 8mg increased from 2001 to 2002 after which it decreased from 2002 to 2006. The CPI is <1 for the entire study period, giving us an indication of low usage and low cost.

The intoduction of Disprin Plus® tablets to the market, did not have a significant influence on the prevalence or cost of Codis® tablets. Disprin Plus® tablets and its innovator, Codis® tablets, had a similar average cost in 2006.

The effect sizes (d-values) calculated between the average cost per medicine item for Codis® Tablets for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005 and 2005-2006 were of no practical significance (d<0.8).

5.3.3.4 Aspirin 200mg/ Paracetamol 200mg/ Chlorphenoxamine HCL 2mg/ Codeine phosphate 15mg/ Caffeine 50mg/ Phenobarbitone 5mg

According to the database, there was only one Aspirin 200mg, Paracetamol 200mg, Chlorphenoxamine HCL 2mg, Codeine phosphate 15mg, Caffeine 50mg and Phenobarbitone 5mg innovator combination analgesic product, Analgen SA ® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.15.

Table 5.15 Prevalence and cost of individual medicine items containing Aspirin 200mg, Paracetamol 200mg, Chlorphenoxamine HCL 2mg, Codeine phosphate 15mg, Caffeine 50mg and Phenobarbitone 5mg for the period 2001, 2002, 2004 and 2005.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Analgen SA® Tab (S5)	402	151.60 ± 104.25	60942.22	0.15	0.32	2.16
2002	Innovator	Analgen SA® Tab (S5)	311	197.69 ± 125.72	61480.98	0.10	0.25	2.49
2004	Innovator	Analgen SA® Tab (S5)	9	283.45 ± 345.49	2551.01	0.00	0.01	5.08
2005	Innovator	Analgen SA® Tab (S5)	1	111.80 ± 0.00	111.80	0.00	0.00	2.21

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive. The prevalence decreased steadily from 2001 to 2005, representing 0.15% of all combination analgesics in 2001 an 0.00% in 2005. This was possibly because of the cost increase from 2001 to 2004.

The average cost increased from R151.60 ± 104.25 in 2001 to R283.45 ± 345.49 in 2004.In 2005 Analgen SA® Tablets was only one time prescribed. The effect sizes (d-values) calculated between the average cost per medicine item for Codis® Tablets for the periods 2001 to 2002 and 2002 to 2005 were of no practical significance (d<0.8).

Analgen SA® Tablets was not prescribed during 2006.

5.3.3.5 Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate 4mg

The results reveal that there was only one Aspirin 37.5mg, Paracetamol 325mg and Codeine phosphate 4mg innovator combination analgesic product, Paincod® Tablets, claimed from 2001 to 2006. The cost and prevalence of this analgesic combination is described in Table 5.16.

Table 5.16 Prevalence and cost of individual medicine items containing Aspirin 37.5mg, Paracetamol 325mg and Codeine phosphate 4mg for the periode 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Generic	Paincod® Tab (S2)	1098	68.16 ± 7.39	74837.61	0.42	0.40	0.95
2002	Generic	Paincod® Tab (S2)	561	74.77 ± 12.21	41946.91	0.18	0.17	0.95
2004	Generic	Paincod® Tab (S2)	195	42.50 ± 8.76	8287.19	0.05	0.04	0.78
2005	Generic	Paincod® Tab (S2)	61	33.83 ± 10.40	2063.39	0.02	0.01	0.72
2006	Generic	Paincod® Tab (S2)	17	25.66±12.00	436.17	0.01	0.00	0.50

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence decreased steadily from 2001 to 2006, representing 0.42% of all combination analgesics in 2001 an 0.01% in 2006. The CPI is < 1 for the entire study period, giving us an indication that the therapy utilised is not very expensive. In 2001 and 2002, the CPI was near to one, but decreased steadily throughout the study indicating a decrease in cost and utilisation.

The average cost increased from 2001 to 2002 but decreased thereafter. The effect sizes (d-values) calculated between the average cost per medicine item Paincod® Tablets for the periods 2002 to 2006 showed practical significance (d>0.8).

5.3.3.6 Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg

The results in Table 5.17 reveal that there was only one Aspirin 200mg, Paracetamol 200mg, Codeine phosphate 15mg and Caffeine 50mg innovator combination analgesic product, Analgen® Tab, claimed through the database. The cost and prevalence of this analgesic combination is described in Table 5.17.

Table 5.17 Prevalence and cost of individual medicine items containing Aspirin 200mg, Paracetamol 200mg, Codeine phosphate 15mg and Caffeine 50mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Analgen® Tab (S2)	120	73.28 ± 60.09	8794.07	0.05	0.05	0.94
2002	Innovator	Analgen® Tab (S2)	158	84.24 ± 47.48	13310.55	0.05	0.05	1.08
2004	Innovator	Analgen® Tab (S2)	167	84.72 ± 63.76	14148.14	0.04	0.07	1.66
2005	Innovator	Analgen® Tab (S2)	126	65.06 ± 80.88	8197.93	0.04	0.06	1.44
2006	Innovator	Analgen® Tab (S2)	9	57.43±54.20	516.88	0.01	0.01	0.59

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Analgen® Tab increased from 2001 to 2004, and decreased from 2004 to 2006, corresponding with the prescription patterns of the total database. The CPI is > 1 from 2002 to 2005, giving us an indication that the therapy utilised was very expensive, before the prevalence and cost decreased from 2005 to 2006.

The effect sizes (d-values) calculated between the average cost per medicine item for Analgen® Tablets for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005 and 2005 to 2006 were of no practical significance (d<0.8).

5.3.3.7 Aspirin/ Paracetamol/ Caffeine

According to the database, there was only one aspirin, paracetamol and caffeine innovator combination analgesic product, Aspirin Co®, claimed. The cost and prevalence of the aspirin, paracetamol and caffeine analgesic combination is described in Table 5.18.

Table 5.18 Prevalence and cost of individual medicine items containing Aspirin, Paracetamol and Caffeine for the period 2001, 2002 and 2004.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Aspirin Co® (S0)	19	3.09 ± 1.25	58.65	0.01	0.00	0.03
2002	Innovator	Aspirin Co® (S0)	8	4.84 ± 1.84	38.69	0.00	0.00	0.06
2004	Innovator	Aspirin Co® (S0)	2	1.36 ± 0.00	2.72	0.00	0.00	0.02

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The product has a very low percentage prevalence and cost of 0.00% for the period 2002 to 2004. Furthermore, the CPI is <1 for all three years, giving us an indication of low usage and low cost. Aspirin Co® was not prescribed in 2005 or 2006.

The average cost per medicine item increased from 2001 to 2002 after which it decreased between 2002 and 2004. The effect sizes (d-values) calculated between the average cost per medicine item of Aspirin Co® Tablets for the periods 2001 to 2002 and 2002 to 2004 showed practical significancant differences (d>0.8).

5.3.3.8 Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg

According to the database, there was only one Aspirin 200mg, Paracetamol 200mg, Codeine phosphate 10mg, Caffeine 30mg and Meprobamate 150mg innovator combination analgesic product, Tenston® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.19.

Table 5.19 Prevalence and cost of individual medicine items containing Aspirin 200mg, Paracetamol 200mg, Codeine phosphate 10mg, Caffeine 30mg and Meprobamate 150mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Tenston® Tab (S5)	966	88.03 ± 54.71	85040.83	0.37	0.45	1.22
2002	Innovator	Tenston® Tab (S5)	851	108.07 ± 68.53	91969.32	0.27	0.37	1.38
2004	Innovator	Tenston® Tab (S5)	1130	77.00 ± 57.12	87010.25	0.30	0.41	1.36
2005	Innovator	Tenston® Tab (S5)	1124	64.21 ± 40.16	72170.60	0.40	0.51	1.26
2006	Innovator	Tenston® Tab (S5)	332	84.92±85.28	28193.45	0.18	0.32	1.78

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Tenston® Tab decreased from 2001 to 2002, after which an increase was seen from 2002 to 2005. From 2005 to 2006 the prevalence decreased. Tenston® Tab represented 0.37% in 2001, 0.27% in 2002, 0.30% in 2004, 0.40% in 2005 and 0.18 % of all combination analgesic medicine items prescribed in the corresponding years.

Meprobamate is a specified schedule 5 active ingredient, therefore is controlled by strict regulations. Specified schedule 5 substances were subject to additional control in terms of section 22A of the Medicines and Related

Substances Act as required under the provisions of the 1971 Convention on Psychotropic Substances (S.A. 2003).

The average cost per analgesic medicine items increased from R88.03 ± 54.71 to R 108.07 ± 68.53 from 2001 to 2002. From 2002 to 2004 the average cost decreased to R77.00 ± 57.12 and from 2004 to 2005 it decreased further to R64.21 ± 40.16. The effect sizes (d-values) calculated between the average cost per medicine item for Tenston® Tablets for the periods 2001 to 2002, 2002 to 2004, 2004 to 2005 and of 2005 to 2006 were of no practical significance (d<0.8).

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.9 Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg

According to the database, there was only one Dextropropoxyphene HCl 65mg, Paracetamol 300mg and Caffeine 30mg innovator combination analgesic product, Doxypol® capsules, claimed. The cost and prevalence of this analgesic combination is described in Table 5.20.

Table 5.20 Prevalence and cost of individual medicine items containing Dextropropoxyphene HCl 65mg, Paracetamol 300mg and Caffeine 30mg for the period 2001, 2002 and 2004.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence%	Cost %@	CPI
2001	Innovator	Doxypol® Cap (S5)	177	41.40 ± 25.79	7328.08	0.07	0.04	0.56
2002	Innovator	Doxypol® Cap (S5)	771	48.72 ± 28.48	37559.41	0.24	0.15	0.63
2004	Innovator	Doxypol® Cap (S5)	24	28.78 ± 11.28	690.74	0.01	0.00	0.32

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Doxypol® capsules increased quite drastically from 2001 to 2002, representing 0.07% in 2001 and 0.24% in 2002 of all combination analgesic medicine items prescribed. The number of Doxypol® medicine items decreased from 0.24% to 0.01% between 2002 and 2004.

The effect sizes (d-values) calculated between the average cost per medicine item for Doxypol® capsules for the periods 2001 to 2002 and 2002 to 2004 were of no practical significance (d<0.8).

The CPI is <1 for all three years, giving us an indication of low usage and low cost. Doxypol® capsules were not prescribed during 2005 or 2006.

5.3.3.10 Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg

According to the database, there was only one Dextropropoxyphene HCl 65mg, Paracetamol 400mg and L-glutamine 25mg innovator combination analgesic product, Lentogesic® Capsules, claimed. The cost and prevalence of this analgesic combination is described in Table 5.21.

Table 5.21 Prevalence and cost of individual medicine items containing Dextropropoxyphene HCl 65mg, Paracetamol 400mg and L-glutamine 25mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Lentogesic® Cap (S5)	8849	183.78 ± 113.60	1626255.91	3.38	8.65	2.56
2002	Innovator	Lentogesic® Cap (S5)	9974	201.31 ±123.90	2007845.92	3.14	8.14	2.59
2004	Innovator	Lentogesic® Cap (S5)	10047	159.72 ± 117.64	1604744.87	2.63	7.54	2.87
2005	Innovator	Lentogesic® Cap (S5)	6285	154.16 ± 107.52	968906.27	2.23	6.79	3.05
2006	Innovator	Lentogesic® Cap (S5)	3642	175.21±110.21	638117.69	1.94	7.26	3.74

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence increased steadily from 2001 to 2004, and decreased from 2004 to 2006, corresponding with the general prescribing patterns on the total database. Lentogesic® Capsules represented 3.38% of all combination analgesic medicine items on the total database in 2001, but only 2.23% in 2005. The decrease in prevalence might me due to the increased availability of more cost-effective combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Lentogesic ® Capsules.

After an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2004, probably due to the implementation of the new price structure in 2004. The effect size (d-values) calculated between the average cost per medicine item for Lentogesic® capsules for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive. Lentogesic® Capsules was one of the top ten combination analgesic prescribed between 2002 and 2006.

5.3.3.11 Ibuprofen 200mg/ Paracetamol 250mg

According to the database, there was two Ibuprofen 200mg and Paracetamol 250mg innovator combination analgesic products, namely Lotem® Suspension and Mypaid® Capsules, claimed from 2001 to 2004. In 2005 the generic, Ibupain® Tablets, was introduced to the market. In 2006 Ibumol® Grape and Ibumol® banana suspensions were also released on the market. The cost and prevalence of these analgesic combinations are described in Table 5.22.

Table 5.22 Prevalence and cost of individual medicine items containing Ibuprofen 200mg and Paracetamol 250mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Lotem® Sus (S2)	9048	47.46 ± 11.19	429392.20	3.45	2.28	0.66
	Innovator	Mypaid® Cap (S2)	15819	63.78 ± 22.04	1008997.49	6.04	5.37	0.89
2002	Innovator	Lotem® Sus (S2)	10942	56.44 ± 13.55	617560.10	3.44	2.50	0.73
	Innovator	Mypaid® Cap (S2)	17796	73.24 ± 26.04	1303397.43	5.60	5.29	0.94
2004	Innovator	Lotem® Sus (S2)	12808	51.58 ± 13.52	660617.27	3.35	3.10	0.93
	Innovator	Mypaid® Cap (S2)	17800	57.29 ± 25.64	1019839.86	4.66	4.79	1.03
2005	Innovator	Lotem® Sus (S2)	8967	50.12 ±11.86	449450.22	3.18	3.15	0.99
	Innovator	Mypaid® Cap (S2)	12148	48.97 ±23.15	594873.83	4.31	4.17	0.97
	Generic	Ibupain® Tab (S2)	3306	11.10 ±19.24	36683.75	1.17	0.26	0.22
2006	Innovator	Lotem® Sus (S2)	4236	51.72±10.78	219079.19	2.26	2.49	1.10
	Innovator	Mypaid® Cap (S2)	1600	33.55±29.56	53687.16	0.85	0.61	0.72
	Generic	Dentopain® Tab (S2)	46	29.91±11.73	1375.93	0.02	0.02	0.78
	Generic	Ibumol® Banana Sus (S2)	978	44.57±6.63	43593.12	0.52	0.50	0.95
	Generic	Ibumol® Grape Sus (S2)	762	43.05±9.43	32800.41	0.41	0.37	0.91
	Generic	Ibupain® Tab (S2)	11848	9.75±20.00	115566.69	6.31	1.31	0.21

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of both Lotem® Suspension and Mypaid® Capsules decreased from 2001 to 2006. In 2005, Ibupain® Tablets and in 2006, Ibumol® Grape and Ibumol® banana suspension were introduced to the market, probably contributing in the decrease in Mypaid® Capsules and Lotem® Suspension prescribing.

After an increase from 2001 to 2002, the average cost per Lotem® Suspension or Mypaid® Capsules decreased from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-

Msimang, 2004:5) and the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

After the introduction of Ibupain® Tablets in 2004 the average cost of Mypaid® Capsules decreased from R57.29 ± 25.64 to R33.55±29.56 between 2004 and 2006. For 2006 the average cost for the newly introduced Ibupain® Tablets was R9.75 ±20.00, representing approximately a third of the price for Mypaid® Capsules. This also contributed to the decrease in cost and prevalence of Mypaid® Capsules from 2005 to 2006.

The effect size (d-values) calculated between the average cost per medicine item for Mypaid® capsules for the period 2001 to 2006 is of no practical significance (d<0.8).

The CPI for all items, except for Mypaid® Capsules in 2004 and Lotem® Suspension in 2006 was less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.12 Ibuprofen 400mg/ Paracetamol 325mg

According to the database, there was only one Ibuprofen 400mg and Paracetamol 325mg innovator combination analgesic product, Mypaid Forte® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.23.

Table 5.23 Prevalence and cost of individual medicine items containing Ibuprofen 400mg and Paracetamol 325mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Mypaid Forte® Tab (S5)	545	66.42 ± 24.75	36198.93	0.21	0.19	0.92
2002	Innovator	Mypaid Forte® Tab (S5)	5448	76.65 ± 29.46	417613.43	1.71	1.69	0.99
2004	Innovator	Mypaid Forte® Tab (S5)	5911	60.94 ± 26.53	360206.74	1.55	1.69	1.09
2005	Innovator	Mypaid Forte® Tab (S5)	4290	57.60 ± 22.05	247095.32	1.52	1.73	1.14
2006	Innovator	Mypaid Forte® Tab (S5)	2783	63.08±22.97	175539.69	1.48	2.00	1.35

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The CPI for Mypaid Forte® Tablets increased from 2001 to 2006. From 2004 to 2006 the CPI was > 1 giving us an indication that the therapy utilised is very expensive. The prevalence decreased steadily from 2002 to 2006, representing 1.71% of all combination analgesics in 2002 and 1.48% in 2006.

The average cost for Mypaid Forte® Tablets fluctuated between 2001 and 2006, increasing from 2001 to 2002, decreasing from 2002 to 2005 and

increasing again from 2005 to 2006. The fluctuation in average cost might be due to the changes in the drug pricing system between 2004 and 2006, as well as the implementation of the Generic Substitution Guidelines in April 2003 (South Africa, 2003:MAE30).

The effect size (d-values) calculated between the average cost per medicine item for Mypaid Forte® tablets for the period 2001 to 2006 is of no practical significance (d<0.8).

5.3.3.13 Ibuprofen 200mg/ Paracetamol 250mg/ Codeine phosphate 10mg

According to the database, there were multiple Ibuprofen 200mg, Paracetamol 250mg and Codeine phosphate 10mg innovator combination analgesic products claimed. The innovator, Ibuflex® Compound, was only present in 2001, and in 2005 the generics Mybulen® Capsules, Gen-payne® Capsules and Ibupain Forte® Capsules was introduced to the market. In 2006 Dentopain Forte® was released. The cost and prevalence of this analgesic combination is described in Table 5.24.

Table 5.24 Prevalence and cost of individual medicine items containing Ibuprofen 200mg, Paracetamol 250mg and Codeine phosphate 10mg for the period 2001, 2002, 2004. 2005 and 2006.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Myprodol® Cap (S3)	60631	91.84 ± 38.67	5568327.54	23.16	29.62	1.28
	Innovator	Myprodol® Sus (S3)	13849	59.25 ± 20.91	820537.63	5.57	4.36	0.78
	Innovator	Ibufiex® Compound (S3)	3	62.75 ± 30.54	188.26	0.00	0.00	0.00
2002	Innovator	Myprodol® Cap (S3)	64455	96.56 ± 44.66	6224029.12	20.27	25.24	1.25
	Innovator	Myprodol® Sus (S3)	15696	70.95 ± 23.42	1113658.44	4.94	4.52	0.91
2004	Innovator	Myprodol® Cap (S3)	85575	65.41 ± 29.29	5597453.57	22.44	26.29	1.17
	Innovator	Myprodol® Sus (S3)	16841	61.08 ± 22.57	1028663.77	4.41	4.83	1.10
2005	Innovator	Mybulen® Sus (S3)	29	38.01 ± 8.08	1102.42	0.01	0.01	0.77
	Innovator	Myprodol® Cap (S3)	51671	67.19 ± 30.24	3471674.53	18.35	24.34	1.33
	Innovator	Myprodol® Sus (S3)	14683	62.83 ± 21.46	922602.48	5.22	6.47	1.24
	Innovator	Myprodol® Tab (S3)	290	73.15 ± 20.78	21212.84	0.10	0.15	1.49
	Generic	Mybulen® Cap (S3)	3338	44.90 ± 19.18	149887.07	1.19	1.05	0.88
	Generic	Gen-payne® (S3)	3109	45.30 ± 19.66	140848.22	1.10	0.99	0.90
	Generic	Ibupain Forte® (S3)	12852	45.06 ± 14.04	579174.77	4.56	4.06	0.89
2006	Innovator	Mybulen® Sus (S3)	6029	50.68±13.90	305531.20	3.21	3.48	1.08
	Innovator	Myprodol® Cap (S3)	7084	55.61±25.54	393906.77	3.77	4.48	1.19
	Innovator	Myprodol® Sus (S3)	3479	54.40±18.27	189270.56	1.85	2.15	1.16
	Innovator	Myprodol® Tab (S3)	857	65.86±23.39	56441.13	0.46	0.64	1.40
	Generic	Dentopain Forte® (S3)	68	33.90±12.32	2305.15	0.04	0.03	0.66
	Generic	Mybulen® Cap (S3)	6025	45.96±24.68	276888.23	3.21	3.15	0.98
	Generic	Gen-payne® Cap (S3)	12053	45.15±13.62	544134.52	6.42	6.19	0.96
	Generic	Ibupain Forte® (S3)	26505	45.39±12.78	1202935.31	14.12	13.68	0.97

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg represented the active ingredient combination with the highest prevalence for the entire study period, increasing from 28.44% (n=74 483) in 2001 to 33.08% (n=62 100) in 2006 of all combination analgesics prescribed (n=261907 for 2001 and n=187 745 for 2006).

Generic substitution influenced the prevalence of the innovator medicine item, Myprodol® Capsules dramatically, causing a decrease from 23.16% (n=60 631) in 2001 to 3.77% (n=7 084) in 2006 representation of all combination analgesic prescribed. In 2006, the generics of Myprodol® Capsules represented 23.79% (n=44 651) of all combination analgesics claimed.

The average cost for the innovator Myprodol® capsules decreased from R91.84 ± 38.67 in 2001 to R55.61±25.54 in 2006. The average cost for each of the products varied between R33.90±12.32 (Dentopain Forte®) and R55.61±25.54 (Myprodol® capsules) in 2006. The effect size (d-values) calculated between the average cost per medicine item for Myprodol® capsules for the period 2001 to 2006 is of practical significance (d>0.8). The effect size (d-values) calculated between the average cost per medicine item for all the other products mentioned above for the period 2001 to 2006 is of practical significance (d<0.8).

The CPI for all innovator items was more than one for the entire study period, giving us an indication that the innovator therapy utilised is quite expensive, while the CPI for all generic items was less than one for the entire study period, giving us an indication that the generic therapy utilised is not very expensive.

5.3.3.14 Ibuprofen 200mg/ Paracetamol 350mg/ Codeine phosphate 10mg

According to the database, there was only one Ibuprofen 200mg, Paracetamol 350mg and Codeine phosphate 10mg generic combination analgesic product, Mybulen® Tablets, claimed. In 2006, Mybucod® was also released. The cost and prevalence of the analgesic combination is described in Table 5.25.

Table 5.25 Prevalence and cost of individual medicine items containing Ibuprofen 200mg, Paracetamol 350mg and Codeine phosphate 10mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Generic	Mybulen® Tab (S3)	14601	66.92 ± 21.62	977076.80	6.04	5.20	0.86
2002	Generic	Mybulen® Tab (S3)	34035	76.23 ± 26.74	2594330.29	10.70	10.52	0.98
2004	Generic	Mybulen® Tab (S3)	50018	48.71 ± 20.33	2436343.51	13.11	11.45	0.87
2005	Generic	Mybulen® Tab (S3)	43940	48.39 ± 19.26	2126139.99	15.60	14.90	0.96
2006	Generic	Mybucod® Tab (S3)	2987	63.63±48.86	190053.61	1.59	2.16	1.36
	Generic	Mybulen® Tab (S3)	29015	53.71±28.67	1558280.58	15.45	17.73	1.15

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Mybulen® Tablets increased steadily from 2001 to 2005 after which it stayed relatively constant between 2005 and 2006. The prevalence percentage increased from 6.04% to 15.45% in 2006.

The average cost per Mybulen® Tablets increased from 2001 to 2002, decreased from 2002 to 2005, after which an increase was seen between 2005 and 2006. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and 2006 (Tshabalala-Msimang, 2006). The effect sizes (d-values) calculated between the average cost per medicine item for Mybulen® Tablets for the periods 2001 to 2006 is of no practical significance (d<0.8).

The CPI is < 1 before 2006, after which it was >1, which gives us an indication that the therapy utilised became more expensive.

5.3.3.15 Ibuprofen 200mg/ Codeine phosphate 10mg

According to the database, there was only one Ibuprofen 200mg and Codeine phosphate 10mg innovator combination analgesic product, Ibucod® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.26.

Table 5.26 Prevalence and cost of individual medicine items containing Ibuprofen 200mg and Codeine phosphate 10mg for the period 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2004	Innovator	Ibucod® Tab (S2)	10	39.98 ± 34.58	399.79	0.00	0.00	0.00
2005	Innovator	Ibucod® Tab (S2)	542	32.13 ± 11.16	17416.91	0.19	0.12	0.64
2006	Innovator	Ibucod® Tab (S2)	377	38.57±11.88	14539.87	0.20	0.17	0.83

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Ibucod® tablets increased between 2004 to 2006, representing 0.00% in 2004 and 0.20% in 2006 of all combination analgesic medicine items prescribed.

The average cost for Ibucod® tablets decreased from 2004 to 2005, probably because of the implementation of the new pricing regulations in 2004 (Tshabalala-Msimang, 2004:5). The effect sizes (d-values) calculated between the average cost per medicine item for Ibucod® tablets for the periods 2004 to 2006 is of no practical significance (d<0.8).

The CPI increased between 2004 and 2006, but is <1 for all three years, giving us an indication of low usage and low cost.

5.3.3.16 Ibuprofen 200mg/ Paracetamol 350mg

From 2004, there was only one Ibuprofen 200mg and Paracetamol 350mg innovator combination analgesic product, Ibumol® Tablets, claimed through the database. The cost and prevalence of Ibumol® Tablets is described in Table 5.27.

Table 5.27 Prevalence and cost of individual medicine items containing Ibuprofen 200mg and Paracetamol 350mg for the period 2004 to 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2004	Innovator	Ibumol® Tab (S2)	86	29.65 ± 10.00	2550.28	0.02	0.01	0.60
2005	Innovator	Ibumol® Tab (S2)	1961	35.33 ± 14.54	69286.59	0.70	0.49	0.69
2006	Innovator	Ibumol® Tab (S2)	1061	35.95±13.86	38141.30	0.57	0.43	0.76

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Ibumol® tablets increased between 2004 to 2005, after which it decreased from 2005 to 2006. Ibumol® tablets represented 0.02% in 2004, 0.70% in 2005 and 0.57% in 2006 of all combination analgesic medicine items prescribed.

The average cost for Ibumol® tablets increased from 2004 to 2006. The effect sizes (d-values) calculated between the average cost per medicine item for Ibumol® tablets for the periods 2004 to 2006 is of no practical significance ($d<0.8$).

The CPI increased between 2004 and 2006, indicating increased usage and cost. But, the CPI is <1 for all three years, giving us an indication of low usage and low cost.

5.3.3.17 Orphenadrine citrate 35mg/ Paracetamol 450mg

There were three Orphenadrine citrate 35mg and Paracetamol 450mg combination analgesic products, namely Norflex Co® Tablets, Besemax® Tablets and Besenol NC® Tablets available on the Interpharm® database from 2001. The cost and prevalence of this analgesic combination is described in Table 5.28.

Table 5.28 Prevalence and cost of individual medicine items containing Orphenadrine citrate 35mg and Paracetamol 450mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Norflex Co® Tab (S2)	4818	37.14 ± 18.50	178922.93	1.84	0.95	0.52
	Generic	Besemax® Tab (S2)	774	38.44 ± 17.75	29752.02	0.30	0.16	0.53
	Generic	Besenol NC® Tab (S2)	79	34.41± 21.63	2718.42	0.03	0.01	0.48
2002	Innovator	Norflex Co® Tab (S2)	6869	43.98 ± 19.88	302078.99	2.16	1.23	0.57
	Generic	Besemax® Tab (S2)	1014	44.02 ± 18.61	44635.73	0.32	0.18	0.57
	Generic	Besenol NC® Tab (S2)	170	43.83 ± 25.04	7450.48	0.05	0.03	0.60
2004	Innovator	Norflex Co® Tab (S2)	9524	37.99 ± 16.54	361788.26	2.49	1.70	0.68
	Generic	Besemax® Tab (S2)	1084	33.93 ± 18.89	36785.04	0.28	0.17	0.62
	Generic	Besenol NC® Tab (S2)	167	33.04 ± 16.37	5518.43	0.04	0.03	0.65
2005	Innovator	Norflex Co® Tab (S2)	9551	34.33 ± 14.96	327883.80	3.39	2.30	0.68
	Generic	Besemax® Tab (S2)	590	28.38 ± 16.27	16746.60	0.21	0.12	0.56
	Generic	Besenol NC® Tab (S2)	89	24.69 ± 14.28	2197.68	0.03	0.02	0.51
2006	Innovator	Norflex Co® Tab (S2)	7720	34.98±13.35	270011.55	4.11	3.07	0.75
	Generic	Besemax® Tab (S2)	140	33.38±23.67	4672.72	0.07	0.05	0.76
	Generic	Besenol NC® Tab (S2)	437	19.96±14.98	8720.83	0.23	0.10	0.43

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Norflex Co® tablets increased steadily from 2001 to 2006, representing 1.84% in 2001 and 4.11% in 2006 of all combination analgesics claimed through the database. The prevalence of Besemax® tablets stayed relatively constant from 2001 to 2004, after which a decrease was seen.

The average costs for Norflex Co® tablets, Besemax® tablets and Besenol NC® tablets were similar between 2001 and 2004, after which each of the products showed a decrease in average cost between 2004 and 2006 due to the implementation of the new price structures (Tshabalala-Msimang, 2004:5). The average cost for Norflex Co® tablets and Besemax® tablets increased between 2005 and 2006, while Besenol NC® tablets showed a larger decrease in average cost, probably causing it's increased prevalence between 2005 and 2006.

The effect size (d-values) calculated between the average cost per medicine item for Norflex Co® tablets, Besemax® tablets and Besenol NC® tablets for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI for all items was less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.18 Paracetamol 100mg/ Aspirin 400mg/ Caffeine 30mg

According to the database, there was only one Paracetamol 100mg, Aspirin 400mg and Caffeine 30mg innovator combination analgesic product, Compral® Headache Tablets, claimed from 2001. The cost and prevalence of Compral® Headache Tablets is described in Table 5.29.

Table 5.29 Prevalence and cost of individual medicine items containing Paracetamol 100mg, Aspirin 400mg and Caffeine 30mg for the period 2001, 2002, 2004 and 2005.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Compral® Headache Tab (S0)	3	14.20± 6.35	42.59	0.00	0.00	0.00
2002	Innovator	Compral® Headache Tab (S0)	9	21.95±12.86	197.58	0.00	0.00	0.00
2004	Innovator	Compral® Headache Tab (S0)	177	29.12±16.51	5153.40	0.05	0.02	0.48
2005	Innovator	Compral® Headache Tab (S0)	36	25.85±14.71	930.58	0.01	0.01	0.65

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Compral® Headache tablets increased from 2001 of 2004, after which it decreased dramatically between 2004 and 2005. It represented a very low percentage usage of 0.00% and 0.01% respectively for 2001 and 2005. Furthermore, the CPI is <1 for the four year period, giving us an indication of low usage and low cost.

The average cost of increase from Compral® Headache tablets 2001 to 2004 after which it decreased. The effect sizes (d-values) calculated between the average cost per medicine item for Compral® Headache tablets for the periods 2001 to 2005 is of no practical significance (d<0.8).

Compral® Headache tablets was discontinued before 2006; this can be a result of the low usage of this medicine product.

5.3.3.19 Paracetamol 500mg/ Chlormezanone 100mg

According to the database, there was one Paracetamol 500mg and Chlormezanone 100mg innovator product, namely Besenol® Tablets and its two generics namely Betaflex® Tab and Myoflex® Tab, claimed during 2001. The cost and prevalence of this analgesic combination is described in Table 5.30.

Table 5.30 Prevalence and cost of individual medicine items containing Paracetamol 500mg and Chlormezanone 100mg for the period 2001.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Besenol® Tab (S2)	1	37.67±0.00	37.67	0.00	0.00	0.00
	Generic	Betaflex® Tab (S2)	5	24.58±4.09	122.88	0.00	0.00	0.00
	Generic	Myoflex® Tab (S2)	2	10.35±1.05	20.70	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

These products all have a very low percentage usage of 0.00% for the year 2001. Furthermore, the CPI is 0.00 giving us an indication of very low usage and cost.

Besenol® tablets and its two generics namely Betaflex® tablets and Myoflex® tablets were not claimed after 2001.

5.3.3.20 Paracetamol 120mg/ Codeine phosphate 5mg

According to the database, there was only one Paracetamol 120mg and Codeine phosphate 5mg innovator combination analgesic product, Infapain® Syrup, claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.29.

Table 5.31 Prevalence and cost of individual medicine items containing Paracetamol 120mg and Codeine phosphate 5mg for the period 2001, 2002, 2004 and 2005.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Infapain® Syr (S2)	37	23.16±7.45	856.87	0.01	0.00	0.24
2002	Innovator	Infapain® Syr (S2)	51	23.32±5.42	1189.42	0.02	0.00	0.24
2004	Innovator	Infapain® Syr (S2)	23	17.01±6.18	391.15	0.01	0.00	0.18
2005	Innovator	Infapain® Syr (S2)	2	19.30±11.70	38.59	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Infapain® syrup increased from 2001 of 2002, after which it decreased dramatically between 2002 and 2005. It represented a very low percentage usage of 0.01% for 2001, 0.02% for 2002 and 0.00 for 2005. Furthermore, the CPI is <1 for the four year period, giving us an indication of low usage and low cost.

The effect sizes (d-values) calculated between the average cost per medicine item for Infapain® syrup for the period 2001 to 2005 is of no practical significance (d<0.8).

Infapain® syrup was discontinued before 2006; this can be a result of the low usage of this medicine product.

5.3.3.21 Paracetamol 320mg/ Codeine phosphate 8mg

There was three Paracetamol 320mg and Codeine phosphate 8mg combination analgesic products, namely Spectrapain®, Painrite® SA and Maxadol® capsules claimed from 2001 to 2002. From 2004 to 2006 only Spectrapain® capsules were still prescribed. The cost and prevalence of this analgesic combination is described in Table 5.32.

Table 5.32 Prevalence and cost of individual medicine items containing Paracetamol 320mg and Codeine phosphate 8mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Spectrapain® Cap (S2)	225	26.70±16.66	6007.19	0.09	0.03	0.36
	Innovator	Painrite® SA Cap (S2)	20	32.09±7.17	641.81	0.01	0.00	0.34
	Generic	Maxadol® Cap (S2)	63	34.20±9.31	2154.31	0.02	0.01	0.57
2002	Innovator	Spectrapain® Cap (S2)	208	27.77±13.98	5775.52	0.07	0.02	0.33
	Innovator	Painrite® SA Cap (S2)	22	35.90±12.15	789.90	0.01	0.00	0.32
	Generic	Maxadol® Cap (S2)	15	35.08±17.57	526.22	0.00	0.00	0.00
2004	Innovator	Spectrapain® Cap (S2)	482	27.70±39.60	13352.95	0.13	0.06	0.48
2005	Innovator	Spectrapain® Cap (S2)	256	19.15±36.09	4901.15	0.09	0.03	0.38
2006	Innovator	Spectrapain® Cap (S2)	59	13.86±7.82	817.98	0.03	0.01	0.31

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Spectrapain® Capsules decreased from 2001 to 2002, increased from 2002 to 2004, after which a decrease was seen between 2004 and 2006.

The average cost for the innovator Spectrapain® Capsules was lower than the average cost for the generic Maxadol® Capsules and the innovator Painrite® SA capsules which were both only prescribed before 2004. The average cost for the innovator Spectrapain® Capsules stayed relatively constant from 2001 to 2004, after which it decreased drastically. This might be due to the implementation of the new price structures in 2004 (Tshabalala-Msimang, 2004:5). The effect sizes (d-value) calculated between the average cost per medicine item for Spectrapain® Capsules for the period 2001 to 2006 is of no practical significance ($d<0.8$). Furthermore, the CPI is <1 for Spectrapain®, Painrite® SA and Maxadol® capsules for the whole study period, giving us an indication of low usage and low cost.

5.3.3.22 Paracetamol 500mg/ Codeine phosphate 10mg

According to the database, there was one innovator and one generic Paracetamol 500mg and Codeine phosphate 10mg combination analgesic product, claimed from 2001 to 2002. From 2004 to 2006, only the innovator, Napacod® tablets, was still prescribed. The cost and prevalence of the analgesic combination is described in Table 5.33.

Table 5.33 Prevalence and cost of individual medicine items containing Paracetamol 500mg and Codeine phosphate 10mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %	Cost %@	CPI
2001	Innovator	Napacod® Tab (S2)	2269	17.76±8.96	40293.31	0.87	0.21	0.25
	Generic	Arcanagesic® Tab (S2)	3	25.77±5.14	77.32	0.00	0.00	0.00
2002	Innovator	Napacod® Tab (S2)	2651	19.45±9.99	51558.86	0.84	0.21	0.25
	Generic	Arcanagesic® Tab (S2)	7	24.17±10.65	169.21	0.00	0.00	0.00
2004	Innovator	Napacod® Tab (S2)	3068	13.42±9.37	41169.44	0.80	0.19	0.24
2005	Innovator	Napacod® Tab (S2)	1663	10.62±12.63	17657.70	0.59	0.12	0.21
2006	Innovator	Napacod® Tab (S2)	1131	11.97±4.01	13538.67	0.60	0.15	0.26

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Napacod® tablets decreased slightly from 2001 to 2004 after which it decreased between 2004 and 2006. This might be due to the implementation of the new price structures in 2004 (Tshabalala-Msimang, 2004:5)

The generic Arcanagesic® Tablets had a very low prevalence percentage of 0.00% for 2001 and 2002 and were not prescribed after 2002. The generic Arcanagesic® Tablets had a higher average cost than the innovator Napacod® tablets, possibly contributing to low prevalence.

After an increase from 2001 to 2002, the average cost for Napacod® tablets decreased from 2002 to 2005, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5).

The effect size (d-values) calculated between the average cost per medicine item for Napacod® tablets for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI for all items were less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.23 Paracetamol 500mg/ Codeine phosphate 20mg

There was only one Paracetamol 500mg and Codeine phosphate 20mg combination analgesic product, namely Empacod® tablets available on the Interpharm® database from 2001. The cost and prevalence of this analgesic combination is described in Table 5.34.

Table 5.34 Prevalence and cost of individual medicine items containing Paracetamol 500mg and Codeine phosphate 20mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Empacod® Tab (S2)	1501	46.60±17.99	69950.25	0.57	0.37	0.65
2002	Innovator	Empacod® Tab (S2)	1122	52.57±20.18	58986.46	0.35	0.24	0.68
2004	Innovator	Empacod® Tab (S2)	719	48.07±26.52	34565.28	0.80	0.16	0.24
2005	Innovator	Empacod® Tab (S2)	323	49.58±28.87	16013.71	0.11	0.11	1.02
2006	Innovator	Empacod® Tab (S2)	176	57.24±27.11	10073.68	0.09	0.11	1.27

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Empacod® tablets increased steadily from 2001 to 2004 after which it decreased between 2004 and 2006. The prevalence percentage increased from 0.57% in 2001 to 0.80% in 2004 and decreased to 0.09% in 2006.

The average cost for Empacod® tablets increased from 2001 to 2002, decreased from 2002 to 2005, after which an increase was seen between 2005 and 2006. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and 2006 (Tshabalala-Msimang, 2006).

The effect sizes (d-values) calculated between the average cost per medicine item for Empacod® tablets for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI is < 1 before 2005, after which it was >1. This gives us an indication that the therapy utilised became more expensive.

5.3.3.24 Paracetamol 500mg/ Codeine phosphate 8mg

The results in Table 5.35 reveal that there was multiple Paracetamol 500mg and Codeine phosphate 8mg combination analgesic products claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.35.

Table 5.35 Prevalence and cost of individual medicine items containing Paracetamol 500mg and Codeine phosphate 8mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Panado® Co Tab (S2)	130	58.53±35.14	7609.46	0.05	0.04	0.81
	Generic	Rocodin® Tab (S2)	15	13.39±6.16	200.92	0.01	0.00	0.11
	Generic	Dolorol Forte® Tab (S2)	2416	30.90±18.86	74655.26	0.92	0.40	0.43
	Generic	Co-gesic® Tab (S2)	58	19.79±49.27	1147.56	0.02	0.01	0.31
	Generic	Famcod® Tab (S2)	12	9.56±1.71	114.75	0.00	0.00	0.00
	Generic	Nitrocod® Tab (S2)	19	16.26±7.47	308.88	0.01	0.00	0.16
	Generic	Painamol® Plus Tab (S2)	674	20.44±8.84	13779.00	0.26	0.07	0.28
2002	Innovator	Panado® Co Tab (S2)	127	57.66±37.83	7323.03	0.04	0.03	0.74
	Innovator	Paincodeine® Tab (S2)	11	30.76±6.80	338.38	0.00	0.00	0.00
	Innovator	Co-Codamol® Eft (S2)	173	28.34±13.30	4902.27	0.05	0.02	0.40
	Generic	Rocodin® Tab (S2)	2	17.95±13.64	35.89	0.00	0.00	0.00
	Generic	Dolorol Forte® Tab (S2)	2377	35.83±22.38	85168.28	0.75	0.35	0.46
	Generic	Co-gesic® Tab (S2)	31	16.99±6.11	526.57	0.01	0.00	0.21
	Generic	Famcod® Tab (S2)	5	11.08±3.06	55.41	0.00	0.00	0.00
	Generic	Nitrocod® Tab (S2)	10	22.47±15.47	224.68	0.00	0.00	0.00
	Generic	Painamol® Plus Tab (S2)	1213	22.46±10.86	27249.76	0.38	0.11	0.29
2004	Innovator	Panado® Co Tab (S2)	107	39.44±18.03	4219.66	0.03	0.02	0.66
	Innovator	Paincodeine® Tab (S2)	162	32.03±12.02	5188.89	0.04	0.02	0.61
	Innovator	Co-Codamol® Eft (S2)	104	27.21±12.17	2829.82	0.03	0.01	0.44
	Generic	Dolorol Forte® Tab (S2)	1568	30.96±20.62	48551.37	0.41	0.23	0.56
	Generic	Nitrocod® Tab (S2)	1	12.19±0.00	12.19	0.00	0.00	0.00
	Generic	Painamol® Plus Tab (S2)	1857	20.01±11.73	37152.02	0.49	0.17	0.36
2005	Innovator	Panado® Co Tab (S2)	68	26.11±7.38	1775.21	0.02	0.01	0.62
	Innovator	Paincodeine® Tab (S2)	39	20.75±10.65	809.06	0.01	0.01	0.57
	Innovator	Co-Codamol® Eft (S2)	5	42.54±19.39	212.72	0.00	0.00	0.00
	Generic	Painamol Plus® Tab (S2)	1096	18.12±10.89	19863.82	0.39	0.14	0.36
	Generic	Dolorol Forte® Tab (S2)	946	31.45±19.47	29751.15	0.34	0.21	0.61
2006	Innovator	Panado® Co Tab (S2)	21	25.94±8.96	544.81	0.01	0.01	0.62
	Innovator	Paincodeine® Tab (S2)	21	17.26±9.92	362.56	0.01	0.00	0.41
	Innovator	Co-Codamol® Eft (S2)	3	35.53±8.92	106.59	0.00	0.00	0.00
	Generic	Painamol Plus® Tab (S2)	430	19.55±13.72	8407.35	0.23	0.10	0.42
	Generic	Dolorol Forte® Tab (S2)	323	30.82±15.91	9954.69	0.17	0.11	0.67

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The generics, Dolorol Forte® tablets and Painamol Plus® tablets, represent the Paracetamol 500mg and Codeine phosphate 8mg combinations with the highest prevalence from 2001 to 2006. The prevalence percentage of Dolorol Forte® tablets decreased from 0.92% to 0.23% of all combination analgesics claimed through the database between 2001 and 2006. Painamol Plus® tablets on the other hand had an increase in prevalence from 2001 to 2004, representing 0.26% in 2001 and 0.49% in 2004 of all combination analgesics claimed. The increased prevalence of Painamol Plus® tablets may be due to the fact that it has a lower average cost and CPI than Dolorol Forte® tablets.

The average cost of Dolorol Forte® tablets and Painamol Plus® tablets stayed relatively constant from 2001 to 2006. Therefore, the effect sizes (d-values) calculated between the average cost per medicine item for Dolorol Forte® tablets and Painamol Plus® tablets for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI for all Paracetamol 500mg and Codeine phosphate 8mg combination analgesic items were less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

Rocodin® tablets, Co-gesic® tablets, Famcod® tablets and Nitrocod® tablets were only prescribed before 2004. This may be due to low utilisation before 2004.

According to De Craen *et al.* (1996:324) paracetamol-codeine preparations produce a significant increase in analgesia compared with paracetamol alone. Multidose studies done by De Craen *et al.*, (1996:324) show an increased occurrence of side effects with paracetamol-codeine combinations. Thus for occasional pain relief a paracetamol-codeine combination might be suitable, but frequent use increases the incidence of side effects.

5.3.3.25 Paracetamol 500mg/ Codeine phosphate 10mg/ Ascorbic acid 50mg

According to the database, there was only one Paracetamol 500mg, Codeine phosphate 10mg and Ascorbic acid 50mg innovator combination analgesic product, Paracetacod® Tablets, claimed from 2001. The cost and prevalence of the analgesic combination is described in Table 5.36.

Table 5.36 Prevalence and cost of individual medicine items containing Paracetamol 500mg, Codeine phosphate 10mg and Ascorbic acid 50mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Paracetacod® Tab (S2)	349	51.03±33.68	17807.93	0.13	0.09	0.73
2002	Innovator	Paracetacod® Tab (S2)	339	56.00±37.38	18982.64	0.11	0.08	0.70
2004	Innovator	Paracetacod® Tab S2)	338	39.43±28.76	13325.79	0.09	0.06	0.70
2005	Innovator	Paracetacod® Tab (S2)	177	26.85±14.67	4751.62	0.06	0.03	0.56
2006	Innovator	Paracetacod® Tab (S2)	102	35.36±23.02	3607.21	0.05	0.04	0.82

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The CPI is < 1 for the entire study period, giving us an indication that the therapy utilised is not very expensive. The prevalence decreased steadily from 2001 to 2006, representing 0.13% of all combination analgesics in 2001 an 0.05% in 2006.

The average cost increased from R51.03 ± 33.68 in 2001 to R56.00 ± 37.38 in 2002 after which the average cost decreased to R35.366 ± 23.02 in 2006. The decrease in average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5). The effect sizes (d-values) calculated between the average cost per medicine item for Paracetacod® Tablets for the period 2001 to 2006 was of no practical significance (d<0.8).

5.3.3.26 Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg

The results in Table 5.17 reveal that there were two Paracetamol 200mg, Codeine phosphate 10mg, Caffeine 30mg and Meprobamate 150mg innovator combination analgesic products, Tenston SA® Tablets and Tenston SA® capsules, claimed from 2001 to 2006. The cost and prevalence of the analgesic combination is described in Table 5.37.

Table 5.37 Prevalence and cost of individual medicine items containing Paracetamol 200mg, Codeine phosphate 10mg, Caffeine 30mg and Meprobamate 150mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Tenston SA® Tab (S5)	6994	104.71±64.82	732312.05	2.67	3.90	1.46
	Innovator	Tenston SA® Cap (S5)	1234	98.36±67.58	121380.13	0.47	0.65	1.37
2002	Innovator	Tenston SA® Tab (S5)	5811	131.80±82.77	765867.19	1.83	3.11	1.70
	Innovator	Tenston SA® Cap (S5)	1213	119.28±77.91	144689.88	0.38	0.59	1.54
2004	Innovator	Tenston SA® Tab (S5)	6456	75.91±61.29	490048.34	1.69	2.30	1.36
	Innovator	Tenston SA® Cap (S5)	1059	93.08±76.78	98570.00	0.28	0.46	1.65
2005	Innovator	Tenston SA® Tab (S5)	5505	62.05±41.11	341563.72	1.96	2.39	1.22
	Innovator	Tenston SA® Cap (S5)	709	78.06±50.30	55347.59	0.25	0.39	1.55
2006	Innovator	Tenston SA® Tab (S5)	1948	68.75±49.90	133930.08	1.04	1.52	1.46
	Innovator	Tenston SA® Cap (S5)	207	80.58±56.94	16679.38	0.11	0.19	1.72

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of both Tenston SA® Tablets and Tenston SA® capsules decreased from 2001 to 2006.

After an increase from 2001 to 2002, the average cost for both Tenston SA® Tablets and Tenston SA® capsules decreased from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). From 2005 to 2006, the average cost for both Tenston SA® Tablets and Tenston SA® capsules increased.

The effect size (d-values) calculated between the average cost per medicine item for both Tenston SA® Tablets and Tenston SA® capsules for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI for both Tenston SA® Tablets and Tenston SA® capsules was more than one for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.27 Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg

According to the database, there were multiple Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg combination

analgesic products claimed from 2001. The cost and prevalence of these analgesic combinations are described in Table 5.38.

Table 5.38 Prevalence and cost of individual medicine items containing Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Stilpane® Cap (S5)	3683	63.34±40.50	233297.93	1.41	1.24	0.88
	Innovator	Stopayne ® Cap (S5)	2738	86.76±55.44	237548.77	1.05	1.26	1.20
	Innovator	Stopayne ® Tab (S5)	1997	66.45±55.67	132693.38	0.76	0.71	0.93
	Innovator	Supragesic® Cap (S5)	87	56.74±28.21	4936.63	0.03	0.03	0.88
	Generic	Antipyn® Forte Tab (S5)	2955	18.89±13.75	55820.03	1.13	0.30	0.26
	Generic	Ban Pain® Tab (S5)	110	16.00±11.51	1759.88	0.04	0.01	0.23
	Generic	Goldgesic® Tab (S5)	93	13.71±7.71	1275.45	0.04	0.01	0.17
	Generic	Go-pain® Tab (S5)	213	19.05±12.38	4057.51	0.08	0.02	0.27
	Generic	Megapyn® Tab (S5)	892	16.12±9.77	14378.16	0.34	0.08	0.22
	Generic	Mepromol® Tab (S5)	102	34.96±17.73	3565.42	0.04	0.02	0.47
	Generic	Noralget® Tab (S5)	1	14.99±0.00	14.99	0.00	0.00	0.00
	Generic	Painagon® Tab (S5)	1959	15.71±7.26	30780.94	0.75	0.16	0.22
	Generic	Pynmed® Tab (S5)	643	17.68±9.38	11365.74	0.25	0.06	0.24
	Generic	Salterpyn® Tab (S5)	1590	19.85±14.09	31568.73	0.61	0.17	0.28
	Generic	Spectrapyn Forte® Cap (S5)	851	51.55±33.00	43866.58	0.32	0.23	0.73
	Generic	Spectrapyn Forte® Tab (S5)	210	15.06±10.43	3161.63	0.08	0.02	0.21
	Generic	Stilpane® Tab (S5)	24570	19.95±12.52	490165.72	9.38	2.61	0.28
	Generic	Vacudol Forte® Tab (S5)	49	14.18±7.01	694.92	0.02	0.00	0.18
	Generic	Xeramax T® (S5)	30	16.11±7.04	483.19	0.01	0.00	0.26
	Generic	Xerogesic® Tab (S5)	115	37.27±25.58	4286.54	0.04	0.02	0.57
2002	Innovator	Stilpane® Cap (S5)	3715	75.44±48.87	280262.77	1.17	1.14	0.97
	Innovator	Stopayne ® Cap (S5)	3277	101.62±64.57	333017.28	1.03	1.35	1.31
	Innovator	Stopayne ® Tab (S5)	1427	81.73±77.08	116622.69	0.45	0.47	1.05
	Innovator	Supragesic® Cap (S5)	97	73.54±48.08	7133.85	0.03	0.03	0.96
	Generic	Adco-Payne® Tab (S5)	61	15.92±7.37	970.96	0.02	0.00	0.20
	Generic	Antipyn® Forte Tab (S5)	2451	21.42±13.48	52507.23	0.77	0.21	0.28
	Generic	Ban Pain® Tab (S5)	45	21.17±13.20	952.68	0.01	0.00	0.39
	Generic	Goldgesic® Tab (S5)	102	14.75±7.58	1504.42	0.03	0.01	0.20
	Generic	Go-pain® Tab (S5)	267	17.11±8.67	4568.30	0.08	0.02	0.23
	Generic	Megapyn® Tab (S5)	578	16.86±10.66	9746.31	0.18	0.04	0.22
	Generic	Mepromol® Tab (S5)	140	35.55±22.53	4976.44	0.04	0.02	0.50
	Generic	Noralget® Tab (S5)	6	12.32±1.97	73.91	0.00	0.00	0.00
	Generic	Painagon® Tab (S5)	2280	15.51±7.70	35353.34	0.72	0.14	0.20
	Generic	Pynmed® Tab (S5)	668	20.50±15.35	13695.14	0.21	0.06	0.26
	Generic	Salterpyn® Tab (S5)	1176	19.34±10.02	22738.15	0.37	0.09	0.25
	Generic	Spectrapyn Forte® Cap (S5)	836	60.48±39.18	50563.09	0.26	0.21	0.79

Table 5.38 (continue) Prevalence and cost of individual medicine items containing Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2002	Generic	Spectrapyn Forte® Tab (S5)	174	15.96±8.39	2776.97	0.05	0.01	0.23
	Generic	Stilpane® Tab (S5)	33012	20.70±13.19	683184.82	10.38	2.77	0.27
	Generic	Vacudol Forte® Tab (S5)	54	20.78±10.30	1122.02	0.02	0.00	0.23
	Generic	Xeramax T® Tab (S5)	45	16.73±7.08	752.86	0.01	0.00	0.31
	Generic	Xerogesic® Tab (S5)	90	37.75±25.19	3397.15	0.03	0.01	0.46
2004	Innovator	Fevapar® Tab (S5)	193	9.20±5.19	1775.28	0.05	0.01	0.17
	Innovator	Stilpane® Cap (S5)	5166	45.75±34.67	236359.69	1.35	1.11	0.82
	Innovator	Stopayne ® Cap (S5)	3239	93.89±64.55	304117.38	0.85	1.43	1.68
	Innovator	Stopayne ® Tab (S5)	1405	80.88±73.59	113633.70	0.37	0.53	1.44
	Innovator	Supragesic® Cap (S5)	63	47.98±29.76	3023.03	0.02	0.01	0.71
	Generic	Adco-Payne® Tab (S5)	202	13.95±5.91	2817.34	0.05	0.01	0.26
	Generic	Antipyn® Forte Tab (S5)	1921	17.62±11.11	33846.85	0.50	0.16	0.32
	Generic	Ban Pain® Tab (S5)	9	23.28±20.63	209.48	0.00	0.00	0.00
	Generic	Goldgesic® Tab (S5)	29	11.29±6.13	327.36	0.01	0.00	0.15
	Generic	Go-pain® Tab (S5)	658	12.38±13.28	8342.93	0.17	0.04	0.23
	Generic	Megapyn® Tab (S5)	307	11.09±7.52	3405.12	0.08	0.02	0.20
	Generic	Mepromol® Tab (S5)	593	17.99±16.57	10669.86	0.16	0.05	0.31
	Generic	Painagon® Tab (S5)	3663	12.66±7.69	46359.74	0.96	0.22	0.23
	Generic	Pynmed® Tab (S5)	30	14.04±7.53	421.22	0.01	0.00	0.20
	Generic	Salterpyn® Tab (S5)	3758	11.21±7.58	42123.93	0.98	0.20	0.20
	Generic	Spectrapyn Forte® Cap (S5)	857	41.35±31.48	35439.75	0.22	0.17	0.76
	Generic	Spectrapyn Forte® Tab (S5)	1036	10.32±16.02	10688.43	0.27	0.05	0.19
	Generic	Stilpane® Tab (S5)	35764	15.54±11.63	555650.21	9.37	2.61	0.28
	Generic	Vacudol Forte® Tab (S5)	5	8.79±1.67	43.95	0.00	0.00	0.00
	Generic	Xeramax T® Tab (S5)	5	3.89±3.48	19.43	0.00	0.00	0.00
	Generic	Xerogesic® Tab (S5)	55	26.07±17.18	1434.02	0.01	0.01	0.67

Table 5.38 (continue) Prevalence and cost of individual medicine items containing Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2005	Innovator	Fevapar® Tab (S5)	1554	10.57±2.67	16429.23	0.55	0.12	0.21
	Innovator	Stilpane® Cap (S5)	3105	40.93±27.31	127087.49	1.10	0.89	0.81
	Innovator	Stopayne ® Cap (S5)	1197	74.37±60.89	89021.46	0.43	0.62	1.45
	Innovator	Stopayne ® Tab (S5)	825	60.99±55.59	50318.52	0.29	0.35	1.22
	Innovator	Supragesic® Cap (S5)	97	41.22±12.24	3997.92	0.03	0.03	0.93
	Generic	Adco-Payne® Tab (S5)	155	16.81±10.88	2606.10	0.06	0.02	0.30
	Generic	Antipyn® Forte Tab (S5)	1148	14.99±8.96	17209.69	0.41	0.12	0.29
	Generic	Goldgesic® Tab (S5)	10	9.24±2.67	92.39	0.00	0.00	0.00
	Generic	Go-pain® Tab (S5)	278	5.87±2.07	1631.34	0.10	0.01	0.11
	Generic	Megapyn® Tab (S5)	95	9.35±7.99	888.58	0.03	0.01	0.21
	Generic	Mepromol® Tab (S5)	847	18.39±11.12	15576.78	0.30	0.11	0.36
	Generic	Painagon® Tab (S5)	2153	10.55±8.31	22714.66	0.76	0.16	0.21
	Generic	Pynmed® Tab (S5)	15	15.55±8.04	233.18	0.01	0.00	0.16
	Generic	Salterpyn® Tab (S5)	2432	10.32±9.43	25104.11	0.86	0.18	0.20
	Generic	Spectrapyn Forte® Cap (S5)	492	23.32±15.45	11472.49	0.17	0.08	0.47
	Generic	Spectrapyn Forte® Tab (S5)	595	8.22±4.57	4893.46	0.21	0.03	0.16
	Generic	Stilpane® Tab (S5)	20808	14.78±10.86	307506.32	7.39	2.16	0.29
	Generic	Vacudol Forte® Tab (S5)	5	7.78±1.90	38.89	0.00	0.00	0.00
	Generic	Xeramax T® Tab (S5)	3	6.92±1.89	20.75	0.00	0.00	0.00
	Generic	Xerogesic® Tab (S5)	13	23.61±17.29	306.94	0.00	0.00	0.00
2006	Innovator	Fevapar® Tab (S5)	466	10.80±3.56	5031.77	0.25	0.06	0.23
	Innovator	Stilpane® Cap (S5)	1782	51.24±30.91	91309.07	0.95	1.04	1.09
	Innovator	Stopayne ® Cap (S5)	308	65.29±60.20	20109.98	0.16	0.23	1.43
	Innovator	Stopayne ® Tab (S5)	846	93.89±66.77	79431.00	0.45	0.90	2.01
	Innovator	Supragesic® Cap (S5)	54	38.84±2.10	2097.13	0.03	0.02	0.80
	Generic	Adco-Payne® Cap (S5)	3	10.88±5.60	32.65	0.00	0.00	0.00
	Generic	Antipyn® Forte Tab (S5)	1519	17.53±6.94	26628.43	0.81	0.30	0.37
	Generic	Goldgesic® Tab (S5)	16	6.56±3.17	105.01	0.01	0.00	0.12
	Generic	Go-pain® Tab (S5)	33	5.91±1.67	195.00	0.02	0.00	0.11
	Generic	Megapyn® Tab (S5)	24	8.11±3.08	194.69	0.01	0.00	0.22
	Generic	Mepromol® Tab (S5)	1194	15.82±8.07	18886.75	0.64	0.21	0.34
	Generic	Painagon® Tab (S5)	698	12.81±8.65	8940.81	0.36	0.10	0.28
	Generic	Pynmed® Tab (S5)	9	11.62±2.90	104.56	0.00	0.00	0.00
	Generic	Salterpyn® Tab (S5)	698	11.51±6.79	8035.87	0.37	0.09	0.25
	Generic	Spectrapyn Forte® Cap (S5)	235	24.87±13.97	5843.71	0.13	0.07	0.51
	Generic	Spectrapyn Forte® Tab (S5)	313	12.20±20.57	3818.86	0.17	0.04	0.26
	Generic	Stilpane® Tab (S5)	9508	16.51±10.85	156999.11	5.06	1.79	0.35
	Generic	Vacudol Forte® Tab (S5)	52	33.57±15.70	1745.57	0.03	0.02	0.00
	Generic	Xerogesic® Tab (S5)	5	5.71±2.13	28.56	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of the innovators, Stilpane® capsules, Stopayne® capsules and Supragesic® capsules decreased steadily from 2001 to 2006. The prevalence of the innovator Stopayne® tablets also decreased from 2001 to 2005, but showed an increase from 2005 to 2006. The decreasing trend in the prevalence of Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg innovator products might me due to the increased availability of less expensive generics and other combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence further.

Meprobamate is a specified schedule 5 active ingredient, therefore is controlled by strict regulations. Specified schedule 5 substances are subject to additional control in terms of section 22A of the Medicines and Related Substances Act as required under the provisions of the 1971 Convention on Psychotropic Substances (S.A. 2003).

The CPI's of innovator Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg combinations is higher than the CPI's of it's generics. The majority of products has a CPI < 1 for the entire study period, giving us an indication that the therapy utilised is not very expensive.

The average cost for all innovator Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg combinations increased from 2001 to 2002, after which a decrease in the average cost was seen from 2002 to 2005. From 2005 to 2006 the average cost of Stopayne® capsules and Supragesic® capsules decreased further, while the average cost of Stillpane® capsules and Stopayne® tablets increased. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and 2006 (Tshabalala-Msimang, 2006).

The effect size (d-values) calculated between the average costs per medicine item for all Paracetamol 320mg, Codeine phosphate 8mg, Caffeine 32mg and Meprobamate 150mg combinations for the period 2001 to 2006 is of no practical significance (d<0.8).

The variety of meprobamate containg analgesics is troublesome, beacause, according to Charney *et al.* (2006) the properties of meprobamate bear some resemblance to those of the benzodiazepines, but the drug has a distinctly higher potential for abuse and has less selective anti-anxiety effects.

5.3.3.28 Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg

According to the database, there were three different Paracetamol 400mg, Codeine phosphate 8mg, Diphenhydramine HCl 5mg and Caffeine 50mg combination analgesic products, Propain® Tablets, Lenadol® Tablets and Tensolve® claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.39.

Table 5.39 Prevalence and cost of individual medicine items containing Paracetamol 400mg, Codeine phosphate 8mg, Diphenhydramine HCl 5mg and Caffeine 50mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Propain® Tab (S2)	2800	56.68±37.50	158694.32	1.07	0.84	0.79
	Generic	Lenadol® Tab (S2)	940	49.18±25.72	46233.39	0.36	0.25	0.68
	Generic	Tensolve® Tab (S2)	376	35.78±17.15	13451.50	0.14	0.07	0.51
2002	Innovator	Propain® Tab (S2)	4059	63.89±40.81	259313.86	1.28	1.05	0.82
	Generic	Lenadol® Tab (S2)	1204	59.12±29.05	71184.78	0.38	0.29	0.76
	Generic	Tensolve® Tab (S2)	432	37.52±78.03	16210.22	0.14	0.07	0.47
2004	Innovator	Propain® Tab (S2)	3519	47.65±35.55	167686.17	0.92	0.79	0.86
	Generic	Lenadol® Tab (S2)	1089	40.41±25.73	44008.55	0.29	0.21	0.71
	Generic	Tensolve® Tab (S2)	624	27.58±17.86	17210.04	0.16	0.08	0.51
2005	Innovator	Propain® Tab (S2)	500	39.57±35.36	19783.25	0.18	0.14	0.77
	Generic	Lenadol® Tab (S2)	520	37.88±20.41	19696.52	0.19	0.14	0.73
	Generic	Tensolve® Tab (S2)	246	13.04±9.22	3207.02	0.06	0.02	0.25
2006	Innovator	Propain® Tab (S2)	151	35.18±38.23	5312.63	0.08	0.06	0.76
	Generic	Lenadol® Tab (S2)	337	52.70±22.46	17758.55	0.18	0.20	1.12
	Generic	Tensolve® Tab (S2)	79	10.59±9.75	836.78	0.04	0.01	0.24

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Propain® tablets, Lenadol® tablets and Tensolve® tablets increased from 2001 to 2002 after which an decrease was seen between 2002 and 2006. The decrease in prevalence might me due to the increased availability of more cost-effective combination analgesics.

The average cost of Propain® tablets, Lenadol® tablets and Tensolve® tablets increased from 2001 to 2002 after which an decrease was seen between 2002 and 2005. From 2005 to 2006, the average cost of Propain®

tablets and Tensolve® tablets decreased further, while the average cost of Lenadol® Tablets increased. The decrease in average cost between 2002 and 2005 might me due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5).

The effect size (d-values) calculated between the average cost per medicine item for Propain® tablets and Lenadol® tablets for the period 2001 to 2006 is of no practical significance (d<0.8). The effect size (d-values) calculated between the average cost per medicine item for Tensolve® tablets is of practical significance (d>0.8).

The CPI for Propain® Tablets, Lenadol® Tablets and Tensolve® Tablets was less than one for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.29 Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg

There were two Paracetamol 400mg, Codeine phosphate 10mg, Diphenhydramine HCl 5mg, Caffeine 50mg and Phenobarbitone 8mg combination analgesic products, namely Propain Forte® tablets and Propain Forte® capsules available on the Interpharm® database from 2001. The cost and prevalence of this analgesic combination is described in Table 5.40.

Table 5.40 Prevalence and cost of individual medicine items containing Paracetamol 400mg, Codeine phosphate 10mg, Diphenhydramine HCl 5mg, Caffeine 50mg and Phenobarbitone 8mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Propain Forte® Tab (S5)	4446	67.59±37.72	300527.32	1.70	1.60	0.94
	Innovator	Propain Forte® Cap (S5)	795	85.62±53.43	68065.35	0.30	0.36	1.21
2002	Innovator	Propain Forte® Tab (S5)	3565	75.54±42.13	269306.22	1.12	1.09	0.98
	Innovator	Propain Forte® Cap (S5)	666	97.84±60.09	65159.64	0.21	0.26	1.26
2004	Innovator	Propain Forte® Tab (S5)	1897	61.39±45.43	116459.24	0.50	0.55	1.09
	Innovator	Propain Forte® Cap (S5)	456	83.24±57.34	37955.85	0.12	0.18	1.49
2005	Innovator	Propain Forte® Tab (S5)	434	96.69±130.91	41965.01	0.15	0.29	1.96
	Innovator	Propain Forte® Cap (S5)	386	77.10±39.80	29761.02	0.14	0.21	1.49
2006	Innovator	Propain Forte® Tab (S5)	467	100.34±60.55	46856.60	0.25	0.53	2.13
	Innovator	Propain Forte® Cap (S5)	310	94.84±57.15	29400.05	0.17	0.33	1.97

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of both Propain Forte® tablets and Propain Forte® capsules decreased from 2001 to 2005 after which a increase was seen between 2005 and 2006. The decrease in prevalence between 2001 and 2005 might me due to the increased availability of other combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of both Propain Forte® tablets and Propain Forte® capsules.

After an increase from 2001 to 2002, the average cost for both Propain Forte® tablets and Propain Forte® capsules decreased from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). From 2004 to 2006, the average cost for Propain Forte® tablets increased while the average cost for Propain Forte® capsules decreased from 2004 to 2005 after which it increased from 2005 to 2006.

The effect size (d-values) calculated between the average cost per medicine item for both Propain Forte® tablets and Propain Forte® capsules for the period 2001 to 2006 is of no practical significance ($d<0.8$).

The CPI for both Propain Forte® tablets and Propain Forte® capsules was more than one for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.30 Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg

The results in Table 5.471 reveal that there was only one Paracetamol 400mg, Codeine phosphate 8mg, Phenyltoloxamine citrate 12mg and Caffeine 32mg innovator combination analgesic product, Suncodin® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.41.

Table 5.41 Prevalence and cost of individual medicine items containing Paracetamol 400mg, Codeine phosphate 8mg, Phenyltoloxamine citrate 12mg and Caffeine 32mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Suncodin® Tab (S2)	2591	50.00±18.49	129555.93	0.99	0.69	0.70
2002	Innovator	Suncodin® Tab (S2)	3375	57.26±22.62	193240.41	1.06	0.78	0.74
2004	Innovator	Suncodin® Tab (S2)	2703	35.95±30.94	97173.47	0.71	0.46	0.64
2005	Innovator	Suncodin® Tab (S2)	347	9.56±4.15	3318.80	0.12	0.02	0.19
2006	Innovator	Suncodin® Tab (S2)	62	10.61±6.36	657.82	0.03	0.01	0.25

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Suncodin® Tablets increased from 2001 to 2002 after which it decreased drastically from 2002 and 2006. The prevalence percentage increased from 0.99% in 2001 to 1.06% in 2002 and decreased to only 0.03% in 2006.

The average cost for Suncodin® Tablets increased from 2001 to 2002, decreased from 2002 to 2005, after which a slight increase was seen between 2005 and 2006. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and 2006 (Tshabalala-Msimang, 2006).

The effect sizes (d-values) calculated between the average cost per medicine item for Suncodin® tablets for the period 2001 to 2006 is of practical significance (d>0.8).

The CPI is < 1 for the entire study period. This gives us an indication that the therapy utilised has low usage and cost.

5.3.3.31 Paracetamol 120mg/ Codeine phosphate 5mg/ Promethazine HCl 6.5mg

The results in Table 5.42 reveal that there were multiple Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg combination analgesic products claimed from 2001. The cost and prevalence of these analgesic combinations are described in Table 5.42.

Table 5.42 Prevalence and cost of individual medicine items containing Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Propain® Syr (S2)	549	74.72±12.56	23454.78	0.21	0.12	0.59
	Innovator	Stopayne® Syr (S2)	3805	40.50±13.99	154113.92	1.45	0.82	0.57
	Innovator	Stilpane® Syr (S2)	4920	29.82±11.36	146715.09	1.88	0.78	0.42
	Generic	Acustop® Syr (S2)	129	29.95±7.93	3863.49	0.05	0.02	0.41
	Generic	Antipyn® Syr (S2)	1270	29.44±8.32	37383.67	0.48	0.20	0.41
	Generic	Ban Pain® Syr (S2)	1506	29.22±9.35	44005.65	0.58	0.23	0.40
	Generic	Dino-payne® Syr (S2)	1	22.74±0.00	22.74	0.00	0.00	0.00
	Generic	Dynapayne® Syr (S2)	17	14.23±4.91	241.86	0.01	0.00	0.13
	Generic	Goldgesic® Syr (S2)	141	29.80±9.66	4201.52	0.05	0.02	0.45
	Generic	Go-Pain® Syr (S2)	433	28.74±6.34	12445.88	0.17	0.07	0.39
	Generic	Infapain Forte® Syr(S2)	91	29.61±9.62	2694.92	0.03	0.01	0.48
	Generic	Kid-Eeze® Syr (S2)	132	28.17±9.72	3719.02	0.05	0.02	0.40
	Generic	Lentogesic® Syr (S2)	426	37.17±15.80	15835.01	0.16	0.08	0.53
	Generic	Maxadol Forte® Syr(S2)	66	29.76±11.69	1964.47	0.03	0.01	0.35
	Ganeric	Medipyn S® Syr (S2)	65	30.36±6.32	1973.37	0.02	0.01	0.52
	Generic	Megapyn® Syr (S2)	325	29.98±8.31	9742.13	0.12	0.05	0.43
	Generic	Mepromol® Syr (S2)	91	29.94±9.32	2724.61	0.03	0.01	0.48
	Generic	Painagon® Syr (S2)	1017	28.76±7.57	29246.06	0.39	0.16	0.40
	Generic	Pedpain® Syr (S2)	26	35.60±17.80	925.51	0.01	0.00	0.49
	Generic	Pynmed® Syr (S2)	1987	27.83±7.63	55304.00	0.76	0.29	0.39
	Generic	Salterpyn® Syr (S2)	1030	29.07±8.68	29946.46	0.39	0.16	0.41
	Generic	Tenston® Syr (S2)	1262	44.19±11.18	55772.30	0.48	0.30	0.62
	Generic	Vacudol® Syr (S2)	146	28.22±9.73	4120.20	0.06	0.02	0.37
	Generic	Xeramax® Syr (S2)	183	28.22±4.76	5164.70	0.07	0.03	0.39
2002	Innovator	Propain® Syr (S2)	601	43.08±13.30	25891.73	0.19	0.11	0.55
	Innovator	Stopayne® Syr (S2)	3606	47.90±19.59	172737.34	1.13	0.70	0.62
	Innovator	Stilpane® Syr (S2)	5422	29.91±9.38	162187.07	1.71	0.66	0.38
	Generic	Acustop® Syr (S2)	74	31.05±8.62	2297.57	0.02	0.01	0.47
	Generic	Adco-Kiddipayne® Syr	681	29.08±7.39	19802.36	0.21	0.08	0.38
	Generic	Antipyn® Syr (S2)	868	28.58±7.65	24803.24	0.27	0.10	0.37
	Generic	Ban Pain® Syr (S2)	1452	30.41±10.49	44159.26	0.46	0.18	0.39
	Generic	Dynapayne® Syr (S2)	12	14.22±4.56	170.67	0.00	0.00	0.00
	Generic	Goldgesic® Syr (S2)	584	28.71±7.39	16766.06	0.18	0.07	0.38
	Generic	Go-Pain® Syr (S2)	606	28.27±6.78	17129.02	0.19	0.07	0.37
	Generic	Infapain Forte® Syr(S2)	64	34.10±14.29	2182.42	0.02	0.01	0.44
	Generic	Kid-Eeze® Syr (S2)	162	30.65±11.14	4965.42	0.05	0.02	0.40

Table 5.42 (continue) Prevalence and cost of individual medicine items containing Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2002	Generic	Lentogesic® Syr (S2)	459	41.73±16.82	19155.01	0.14	0.08	0.55
	Generic	Maxadol Forte® Syr (S2)	21	30.34±8.47	637.14	0.01	0.00	0.26
	Ganeric	Medipyn S® Syr (S2)	25	34.48±11.18	862.04	0.01	0.00	0.35
	Generic	Megapyn® Syr (S2)	140	32.79±11.39	4590.96	0.04	0.02	0.47
	Generic	Mepromol® Syr (S2)	84	26.35±6.82	2213.38	0.03	0.01	0.30
	Generic	Painagon® Syr (S2)	1498	28.02±7.61	41978.63	0.47	0.17	0.36
	Generic	Pedpain® Syr (S2)	22	27.24±0.88	599.85	0.01	0.00	0.24
	Generic	Pynmed® Syr (S2)	2044	28.72±7.70	58702.46	0.64	0.24	0.37
	Generic	Salterpyn® Syr (S2)	1238	28.82±10.15	35684.80	0.39	0.14	0.37
	Generic	Tenston® Syr (S2)	1356	54.42±16.07	73797.64	0.43	0.30	0.70
	Generic	Vacudol® Syr (S2)	136	28.48±10.31	3873.70	0.04	0.02	0.39
	Generic	Xeramax® Syr (S2)	312	27.20±8.43	8485.62	0.10	0.03	0.34
2004	Innovator	Propain® Syr (S2)	226	34.29±7.56	7748.61	0.06	0.04	0.61
	Innovator	Stopayne® Syr (S2)	3464	40.51±20.27	140322.14	0.91	0.66	0.72
	Innovator	Stilpane® Syr (S2)	6079	18.10±9.74	110014.58	1.59	0.52	0.33
	Generic	Acustop® Syr (S2)	7	54.46±35.05	381.20	0.00	0.00	0.00
	Generic	Adco-Kiddipayne® Syr (S2)	1452	18.61±8.64	27017.60	0.38	0.13	0.33
	Generic	Antipyn® Syr (S2)	30	24.70±7.71	741.06	0.01	0.00	0.35
	Generic	Ban Pain® Syr (S2)	1136	13.91±11.80	15807.20	0.30	0.07	0.25
	Generic	Dynapayne® Syr (S2)	2	13.18±0.00	26.36	0.00	0.00	0.00
	Generic	Fevapar® Syr (S2)	369	14.56±9.83	5373.37	0.10	0.03	0.25
	Generic	Goldgesic® Syr (S2)	613	20.53±9.50	12586.54	0.16	0.06	0.37
	Generic	Go-Pain® Syr (S2)	547	16.44±9.12	8991.89	0.14	0.04	0.30
	Generic	Infapain Forte® Syr (S2)	43	17.71±6.43	761.34	0.01	0.00	0.36
	Generic	Kid-Eeze® Syr (S2)	41	23.10±9.50	947.11	0.01	0.00	0.44
	Generic	Lentogesic® Syr (S2)	290	34.19±15.93	9916.17	0.08	0.05	0.58
	Ganeric	Medipyn S® Syr (S2)	59	14.93±11.22	880.96	0.02	0.00	0.21
	Generic	Megapyn® Syr (S2)	88	17.69±7.57	1556.74	0.02	0.01	0.37
	Generic	Mepromol® Syr (S2)	271	17.15±7.71	4648.78	0.07	0.02	0.31
	Generic	Painagon® Syr (S2)	2368	16.19±8.94	38327.48	0.62	0.18	0.29
	Generic	Pedpain® Syr (S2)	16	16.12±14.55	257.84	0.00	0.00	0.00
	Generic	Pynmed® Syr (S2)	2085	19.86±8.45	41404.66	0.55	0.19	0.35
	Generic	Salterpyn® Syr (S2)	1643	13.58±10.73	22319.65	0.43	0.10	0.24
	Generic	Tenston® Syr (S2)	640	39.05±23.87	24989.31	0.17	0.12	0.69
	Generic	Vacudol® Syr (S2)	50	16.79±10.21	839.34	0.01	0.00	0.39
	Generic	Xeramax® Syr (S2)	41	27.04±12.95	1108.63	0.01	0.01	0.52

Table 5.42 (continue) Prevalence and cost of individual medicine items containing Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2005	Innovator	Propain® Syr (S2)	15	31.64±7.94	474.61	0.01	0.00	0.33
	Innovator	Stopayne® Syr (S2)	1878	29.60±16.41	55582.72	0.67	0.39	0.58
	Innovator	Stilpane® Syr (S2)	4603	13.85±8.20	63729.34	1.63	0.45	0.27
	Generic	Adco-Kiddipayne® Syr (S2)	1297	14.35±4.47	18613.34	0.46	0.13	0.28
	Generic	Antipyn® Syr (S2)	4	15.50±7.04	61.99	0.00	0.00	0.00
	Generic	Ban Pain® Syr (S2)	678	14.35±4.62	9727.95	0.24	0.07	0.28
	Generic	Fevapar® Syr (S2)	415	11.25±3.20	4670.62	0.15	0.03	0.22
	Generic	Goldgesic® Syr (S2)	115	13.90±3.98	1599.02	0.04	0.01	0.00
	Generic	Go-Pain® Syr (S2)	232	9.34±3.55	2166.94	0.08	0.02	0.19
	Generic	Infapain Forte® Syr (S2)	14	15.56±4.08	217.87	0.00	0.00	0.00
	Generic	Kid-Eeze® Syr (S2)	30	11.55±4.08	346.37	0.01	0.00	0.24
	Generic	Lentogesic® Syr (S2)	146	18.70±11.79	2730.44	0.05	0.02	0.38
	Ganeric	Medipyn S® Syr (S2)	20	12.28±10.21	245.51	0.01	0.00	0.17
	Generic	Megapyn® Syr (S2)	26	12.32±4.43	320.21	0.01	0.00	0.22
	Generic	Mepromol® Syr (S2)	451	12.01±3.81	5416.58	0.16	0.04	0.24
	Generic	Painagon® Syr (S2)	1198	9.98±3.39	11959.54	0.43	0.08	0.19
	Generic	Pedpain® Syr (S2)	2	27.99±0.00	55.98	0.00	0.00	0.00
	Generic	Pynmed® Syr (S2)	1388	14.09±3.42	19554.02	0.49	0.14	0.28
	Generic	Salterpyn® Syr (S2)	753	8.06±4.63	6071.12	0.27	0.04	0.16
	Generic	Tenston® Syr (S2)	353	31.14±12.46	10994.05	0.13	0.08	0.59
	Generic	Vacudol® Syr (S2)	9	9.19±5.86	82.72	0.00	0.00	0.00
	Generic	Xeramax® Syr (S2)	5	13.67±8.03	68.34	0.00	0.00	0.00
2006	Innovator	Stopayne® Syr (S2)	547	23.69±13.62	12961.09	0.29	0.15	0.51
	Innovator	Stilpane® Syr (S2)	2735	15.28±9.11	41793.49	1.46	0.48	0.33
	Generic	Adco-Kiddipayne® Syr (S2)	1005	13.97±5.04	14037.47	0.54	0.16	0.30
	Generic	Ban Pain® Syr (S2)	338	15.20±4.48	5136.47	0.18	0.06	0.32
	Generic	Fevapar® Syr (S2)	244	11.99±1.78	2925.72	0.13	0.03	0.26
	Generic	Goldgesic® Syr (S2)	56	7.73±2.28	429.70	0.03	0.00	0.16
	Generic	Go-Pain® Syr (S2)	42	8.75±1.97	367.37	0.02	0.00	0.21
	Generic	Infapain Forte® Syr (S2)	1	32.12±0.00	32.12	0.00	0.00	0.00
	Generic	Kid-Eeze® Syr (S2)	4	9.38±0.59	37.51	0.00	0.00	0.00
	Generic	Lentogesic® Syr (S2)	57	17.60±7.94	1003.07	0.03	0.01	0.38
	Generic	Medipyn S® Syr (S2)	6	7.56±0.01	45.34	0.00	0.00	0.00
	Generic	Megapyn® Syr (S2)	132	15.29±3.20	2018.75	0.07	0.02	0.33
	Generic	Mepromol® Syr (S2)	322	13.38±7.93	4308.30	0.17	0.05	0.29
	Generic	Painagon® Syr (S2)	327	10.53±3.91	3442.04	0.17	0.04	0.23
	Generic	Pynmed® Syr (S2)	1311	15.78±3.23	20693.52	0.70	0.24	0.34
	Generic	Salterpyn® Syr (S2)	208	9.02±2.71	1875.79	0.11	0.02	0.19
	Generic	Tenston® Syr (S2)	47	36.41±6.28	1711.29	0.03	0.02	0.65
	Generic	Vacudol® Syr (S2)	1	13.04±0.00	13.04	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

Stopayne® syrup, Stilpane® syrup, Pynmed® syrup and Ban Pain® syrup were the four products with the highest prevalence from 2001 to 2006. The prevalence of these products decreased from 2001 to 2006. The decrease in prevalence might be due to the increased availability of more cost-effective combination analgesics.

The average costs for all Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg containing products illustrated an increasing trend from 2001 to 2002 and a decreasing trend from 2002 to 2006. The changes in the average cost was probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5).

The CPI for all items containing Paracetamol 120mg, Codeine phosphate 5mg and Promethazine HCl 6.5mg was less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.32 Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg

According to the database, there was only one Dextropopoxyphene 50mg, Diphenhydramine HCl 5mg and Caffeine 50mg innovator combination analgesic product Synap Forte® tablets, claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.43.

Table 5.43 Prevalence and cost of individual medicine items containing Dextropopoxyphene 50mg, Diphenhydramine HCl 5mg and Caffeine 50mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Synap Forte® Tab (S5)	13058	165.27±96.79	2158054.66	5.29	11.48	2.17
2002	Innovator	Synap Forte® Tab (S5)	15533	181.07±107.72	2812513.87	4.88	11.41	2.34
2004	Innovator	Synap Forte® Tab (S5)	18315	129.60±86.39	2373696.43	4.80	11.15	2.32
2005	Innovator	Synap Forte® Tab (S5)	10788	116.00±69.69	1251424.30	3.83	8.77	2.29
2006	Innovator	Synap Forte® Tab (S5)	3752	132.48±84.25	497056.37	2.00	5.65	2.83

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Synap Forte® tablets decreased steadily from 2001 to 2006. Synap Forte® tablets represented 5.29% of all combination analgesic medicine items on the total database in 2001, but only 2.00% in 2006. The

decrease in prevalence might me due to the increased availability of other combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Synap Forte® tablets.

The after an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2005, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). Between 2005 and 2006 the average cost for Synap Forte® tablets increased.

The effect size (d-values) calculated between the average cost per medicine item for Synap Forte® tablets for the period 2001 to 2006 is of no practical significance (d<0.8). The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.33 Paracetamol 12mg/ Doxylamine succinate 5mg

There was only one Paracetamol 12mg and Doxylamine succinate 5mg combination analgesic products, Syndette® syrup available on the Interpharm® database from 2001 to 2004. The cost and prevalence of this analgesic combination is described in Table 5.44.

Table 5.44 Prevalence and cost of individual medicine items containing Paracetamol 12mg and Doxylamine succinate 5mg for the period 2001, 2002 and 2004.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Syndette® Syr (S2)	214	34.68± 6.68	7420.81	0.08	0.04	0.49
2002	Innovator	Syndette® Syr (S2)	183	41.0 ±98.62	7519.55	0.06	0.03	0.51
2004	Innovator	Syndette® Syr (S2)	1	30.21±0.00	30.21	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Syndette® syrup decreased between 2001 and 2004. It represented a very low percentage usage of 0.08% for 2001, 0.06% for 2002 and 0.00 for 2004. Furthermore, the CPI is <1 for the three year period, giving us an indication of low usage and low cost.

The effect sizes (d-values) calculated between the average cost per medicine item for Syndette® syrup for the period 2001 to 2004 is of no practical significance (d<0.8).

Syndette® syrup was discontinued before 2005; this can be a result of the low usage of this medicine product.

5.3.3.34 Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 30mg/ Codeine

According to the database, there were multiple Paracetamol 450mg, Doxylamine succinate 5mg, Caffeine 30mg and Codeine phosphate 10mg combination analgesic products claimed from 2001. The cost and prevalence of these analgesic combinations are described in Table 5.45.

Table 5.45 Prevalence and cost of individual medicine items containing Paracetamol 450mg, Doxylamine succinate 5mg, Caffeine 30mg and Codeine phosphate 10mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Frequency %*	Cost %@	CPI
2001	Innovator	Copa-Dol® Tab (S2)	102	36.17±20.55	3689.02	0.04	0.02	0.49
	Innovator	Pynstop® Tab (S2)	2218	58.61±39.29	130003.29	0.85	0.69	0.81
	Innovator	Syndol® Tab (S2)	1683	61.83±44.04	104059.80	0.64	0.55	0.86
	Innovator	Xerotens® Cap (S2)	196	62.48±48.46	12246.66	0.07	0.07	0.93
	Generic	Abflex-4® Tab (S2)	256	30.72±16.09	7865.23	0.10	0.04	0.42
	Generic	Acurate® Tab (S2)	278	34.66±11.78	9636.68	0.11	0.05	0.47
	Generic	Adco-dol® Tab (S2)	5144	44.40±25.74	228375.37	1.96	1.21	0.62
	Generic	Betapyn® Tab (S2)	3278	66.70±46.16	218653.06	1.25	1.16	0.93
	Generic	Dino-dox® Tab (S2)	1	15.96±0.00	15.96	0.00	0.00	0.00
	Generic	Forpain® Tab (S2)	2	17.13±2.97	34.26	0.00	0.00	0.00
	Generic	Lenapain® Tab (S2)	221	37.10±16.36	8198.72	0.08	0.04	0.55
	Generic	Nomopain® Tab (S2)	312	46.15±33.44	14398.98	0.12	0.08	0.64
	Generic	Paxidal® Tab (S2)	29	30.06±12.01	871.83	0.01	0.00	0.46
	Generic	Sedapain® Tab (S2)	687	42.24±34.93	29021.75	0.26	0.15	0.59
	Generic	Sedinol® Tab (S2)	622	56.51±33.42	35146.24	0.24	0.19	0.78
	Generic	Tensodol® Tab (S2)	244	37.40±20.13	9126.44	0.09	0.05	0.54
	Generic	Tensopyn® Tab (S2)	236	38.36±24.17	9052.42	0.09	0.05	0.54
2002	Innovator	Copa-Dol® Tab (S2)	206	37.16±19.20	7655.00	0.06	0.03	0.52
	Innovator	Pynstop® Tab (S2)	3390	69.04±48.00	234046.27	1.07	0.95	0.89
	Innovator	Syndol® Tab (S2)	2043	67.44±48.95	137774.33	0.64	0.56	0.87
	Innovator	Xerotens® Cap (S2)	139	63.22±31.70	8788.08	0.04	0.04	0.89
	Generic	Abflex-4® Tab (S2)	385	36.02±28.08	13866.45	0.12	0.06	0.47
	Generic	Acurate® Tab (S2)	285	38.39±15.45	10940.43	0.09	0.04	0.49
	Generic	Adco-dol® Tab (S2)	8079	48.35±29.46	390611.38	2.54	1.58	0.62
	Generic	B-Dol® Tab (S2)	12	41.31±38.24	495.77	0.00	0.00	0.00
	Generic	Betapyn® Tab (S2)	5053	69.21±49.36	349730.63	1.59	1.42	0.89
	Generic	Dino-dox® Tab (S2)	2	42.18±18.10	84.36	0.00	0.00	0.00
	Generic	Lenapain® Tab (S2)	441	42.18±24.35	18602.39	0.14	0.08	0.54
	Generic	Nomopain® Tab (S2)	371	52.30±40.80	19404.30	0.12	0.08	0.66
	Generic	Paxidal® Tab (S2)	43	37.09±15.85	1594.67	0.01	0.01	0.65
	Generic	Pynclear® Tab (S2)	34	44.41±11.14	1510.02	0.01	0.01	0.61
	Generic	Sedapain® Tab (S2)	731	45.27±40.32	33091.26	0.23	0.13	0.58
	Generic	Sedinol® Tab (S2)	582	59.13±37.40	34416.44	0.18	0.14	0.78
	Generic	Tensodol® Tab (S2)	489	42.63±23.59	20846.90	0.15	0.08	0.56
	Generic	Tensopyn® Tab (S2)	102	34.01±23.01	3469.49	0.03	0.01	0.47

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Frequency %	Cost %@	CPI
2004	Innovator	Copa-Dol® Tab (S2)	78	24.87±15.87	1939.62	0.02	0.01	0.46
	Innovator	Pynstop® Tab (S2)	3219	47.54±39.90	153030.78	0.84	0.72	0.86
	Innovator	Syndol® Tab (S2)	1672	54.61±49.87	91310.71	0.44	0.43	0.97
	Innovator	Xerotens® Cap (S2)	37	48.57±15.98	1797.18	0.01	0.01	0.84
	Generic	Abflex-4® Tab (S2)	1175	22.99±21.23	27011.14	0.31	0.13	0.41
	Generic	Acurate® Tab (S2)	144	33.50±21.57	4823.72	0.04	0.02	0.57
	Generic	Adco-dol® Tab (S2)	12109	32.66±26.64	395504.64	3.17	1.86	0.59
	Generic	B-Dol® Tab (S2)	776	23.02±17.08	17867.00	0.20	0.08	0.03
	Generic	Betapyn® Tab (S2)	5586	49.33±40.16	275538.42	1.46	1.29	0.89
	Generic	Codoxol® Tab (S2)	4	5.75±1.17	23.00	0.00	0.00	0.00
	Generic	Doxyn® Tab (S2)	2	9.42±5.22	18.84	0.00	0.00	0.00
	Generic	Lenapain® Tab (S2)	998	23.46±20.39	23416.64	0.26	0.11	0.42
	Generic	Nomopain® Tab (S2)	283	24.81±19.59	7020.20	0.07	0.03	0.47
	Generic	Paxidal® Tab (S2)	164	42.27±69.09	6931.74	0.04	0.03	0.81
	Generic	Pynclear® Tab (S2)	97	38.73±17.59	3756.39	0.03	0.02	0.59
	Generic	Sedapain® Tab (S2)	281	38.68±31.81	10869.03	0.07	0.05	0.73
	Generic	Sedinol® Tab (S2)	315	52.55±39.11	16552.35	0.08	0.08	0.97
	Generic	Tensodol® Tab (S2)	729	35.53±24.67	25903.53	0.19	0.12	0.64
	Generic	Tensopyn® Tab (S2)	5	22.90±5.00	114.48	0.00	0.00	0.00
2005	Innovator	Copa-Dol® Tab (S2)	1	47.69±0.00	47.69	0.00	0.00	0.00
	Innovator	Pynstop® Tab (S2)	1673	27.07±25.47	45282.11	0.59	0.32	0.54
	Innovator	Syndol® Tab (S2)	898	33.63±30.40	30199.48	0.32	0.21	0.66
	Innovator	Tensopyn® Eft (S2)	30	32.38±12.42	971.26	0.01	0.01	0.68
	Innovator	Xerotens® Cap (S2)	2	72.25±67.52	144.49	0.00	0.00	0.00
	Generic	Abflex-4® Tab (S2)	1279	19.11±14.47	24438.09	0.45	0.17	0.38
	Generic	Acurate® Tab (S2)	152	26.45±11.42	4020.44	0.05	0.03	0.56
	Generic	Adco-dol® Tab (S2)	9440	22.47±16.63	212081.01	3.35	1.49	0.44
	Generic	B-Dol® Tab (S2)	293	26.10±16.43	7646.14	0.10	0.05	0.54
	Generic	Betapyn® Tab (S2)	3706	44.55±33.59	165115.33	1.32	1.16	0.88
	Generic	Codoxol® Tab (S2)	134	10.65±21.62	1427.64	0.05	0.01	0.20
	Generic	Doxyn® Tab (S2)	2	3.88±5.37	7.76	0.00	0.00	0.00
	Generic	Lenapain® Tab (S2)	224	20.12±14.56	4506.18	0.08	0.03	0.39
	Generic	Nomopain® Tab (S2)	212	30.73±15.58	6513.79	0.08	0.05	0.57
	Generic	Paxidal® Tab (S2)	61	9.51±7.88	580.30	0.02	0.00	0.20
	Generic	Pynclear® Tab (S2)	3	45.67±21.11	137.01	0.00	0.00	0.00
	Generic	Sedapain® Tab (S2)	84	22.55±10.73	1894.20	0.03	0.01	0.44
	Generic	Sedinol® Tab (S2)	117	43.41±32.88	5079.36	0.04	0.04	0.89
	Generic	Tensodol® Tab (S2)	83	21.99±16.53	1825.05	0.03	0.01	0.43
	Generic	Tensopyn® Tab (S2)	42	20.50±11.97	860.85	0.01	0.01	0.60

Table 5.45 (Continue) Prevalence and cost of individual medicine items containing Paracetamol 450mg, Doxylamine succinate 5mg, Caffeine 30mg and Codeine phosphate 10mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator /Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2006	Innovator	Pynstop® Tab (S2)	1151	25.73±26.06	29612.38	0.61	0.34	0.55
	Innovator	Syndol® Tab (S2)	348	41.54±38.88	14455.41	0.19	0.16	0.87
	Innovator	Tensopyn® Eff (S2)	809	34.78±11.78	28134.07	0.43	0.32	0.74
	Generic	Abflex-4® Tab (S2)	1100	27.16±18.17	29877.19	0.59	0.34	0.58
	Generic	Acurate® Tab (S2)	35	25.20±18.58	882.01	0.02	0.01	0.50
	Generic	Adco-dol® Tab (S2)	6532	25.10±17.30	163940.01	3.48	1.86	0.54
	Generic	B-Dol® Tab (S2)	400	31.87±15.47	12748.64	0.21	0.15	0.69
	Generic	Betapyn® Tab (S2)	3043	54.19±34.54	164913.50	1.62	1.88	1.16
	Generic	Codoxol® Tab (S2)	710	7.79±5.77	5527.69	0.38	0.06	0.17
	Generic	Doxyn® Tab (S2)	15	5.23±0.00	78.45	0.01	0.00	0.09
	Generic	Lenapain® Tab (S2)	35	23.62±22.27	826.78	0.02	0.01	0.47
	Generic	Nomopain® Tab (S2)	103	45.56±25.54	4692.56	0.05	0.05	1.07
	Generic	Paxidal® Tab (S2)	153	25.65±16.03	3925.20	0.08	0.04	0.56
	Generic	Sedapain® Tab (S2)	61	27.56±11.71	1681.42	0.03	0.02	0.64
	Generic	Sedinol® Tab (S2)	80	57.72±34.38	4617.65	0.04	0.05	1.31
	Generic	Tensodol® Tab (S2)	22	21.85±19.32	480.59	0.01	0.01	0.55
	Generic	Tensopyn® Tab (S2)	410	19.96±9.37	8183.00	0.22	0.09	0.42

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

Pynstop® tablets, Syndol® tablets, Abflex-4® tablets, Adco-dol® tablets and Betapyn® tablets were the five combination analgesics containing paracetamol 450mg, doxylamine succinate 5mg, caffeine 30mg and codeine phosphate 10mg with the higest prevalence from 2001 to 2006.

The average costs of these five products increased from 2001 to 2002, after which it decreased steadily from 2002 to 2006. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and the increased availability of generic medicine items (South Africa, 2003:MAE30).

Pynstop® tablets, Syndol® tablets, Abflex-4® tablets, Adco-dol® tablets and Betapyn® tablets showed an increase in prevalence from 2001 to 2002. From 2002 to 2006 the prevalence of Abflex-4® tablets and Adco-dol® tablets

increased further, while the prevalence of Pynstop® tablets, Syndol® tablets and Betapyn® tablets decreased.

The effect size (d-values) calculated between the average cost per medicine item for Pynstop® tablets for the period 2001 to 2006 is the only value with practical significance (d>0.8).

The CPI for most items were less than one for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.35 Paracetamol 500mg/ Mephenesin 150mg

The results in Table 5.46 reveal that there was only one Paracetamol 500mg and Mephenisin 150mg innovator combination analgesic product, Spasmend® Tablets, claimed. The cost and prevalence of this analgesic combination is described in Table 5.46.

Table 5.46 Prevalence and cost of individual medicine items containing Paracetamol 500mg and Mephenisin 150mg for the period 2001. 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Spasmend® Tab (S2)	1217	43.90±22.58	53425.66	0.46	0.28	0.62
2002	Innovator	Spasmend® Tab (S2)	1895	50.64±23.64	95960.82	0.60	0.39	0.65
2004	Innovator	Spasmend® Tab(S2)	2987	33.10±17.82	98883.21	0.78	0.46	0.60
2005	Innovator	Spasmend® Tab (S2)	1445	24.35±13.14	35187.00	0.51	0.25	0.48
2006	Innovator	Spasmend® Tab (S2)	669	26.97±18.58	18043.63	0.36	0.21	0.57

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Spasmend® tablets increased steadily from 2001 to 2004 after which it decreased between 2004 and 2006. The prevalence percentage increased from 0.46% in 2001 to 0.78% in 2004 and decreased to 0.36% in 2006.

The average cost for Spasmend® tablets increased from 2001 to 2002, decreased from 2002 to 2005, after which an increase was seen between 2005 and 2006. The fluctuation of the average cost might be due to the new pricing regulations implemented in 2004 (Tshabalala-Msimang, 2004:5) and 2006 (Tshabalala-Msimang, 2006).

The effect sizes (d-values) calculated between the average cost per medicine item for Spasmend® tablets for the period 2001 to 2006 is of no practical significance (d<0.8). 2006. The CPI is < 1 for the entire study period, giving us an indication that the therapy utilised is not very expensive.

5.3.3.36 Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg

There were two Paracetamol 400mg, Codeine phosphate 8mg and Meprobamate 200mg combination analgesic products, Synaleve® Capsules and Trinagesic® Capsules, available on the Interpharm® database from 2001. The cost and prevalence of these analgesic combination are described in Table 5.47.

Table 5.47 Prevalence and cost of individual medicine items containing Paracetamol 400mg, Codeine phosphate 8mg and Meprobamate 200mg for the period 2001. 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence%*	Cost %@	CPI
2001	Innovator	Synaleve® Cap (S5)	861	45.63 ±40.34	39287.10	0.33	0.21	0.63
	Generic	Trinagesic® Cap (S5)	207	66.67±23.84	13801.62	0.08	0.07	0.92
2002	Innovator	Synaleve® Cap (S5)	525	77.53±57.58	40702.58	0.17	0.17	0.97
	Generic	Trinagesic® Cap (S5)	206	67.53±33.87	13910.88	0.06	0.06	0.94
2004	Innovator	Synaleve® Cap (S5)	509	58.82±34.80	29940.79	0.13	0.14	1.08
	Generic	Trinagesic® Cap (S5)	88	35.16±28.02	3094.03	0.02	0.01	0.73
2005	Innovator	Synaleve® Cap (S5)	79	62.46±44.70	4934.46	0.03	0.03	1.15
	Generic	Trinagesic® Cap (S5)	22	19.44±11.32	427.77	0.01	0.00	0.30
2006	Innovator	Synaleve® Cap (S5)	6	28.79±14.21	172.76	0.00	0.00	0.00
	Generic	Trinagesic® Cap (S5)	5	16.18±6.26	80.89	0.00	0.00	0.00

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of both Synaleve® Capsules and Trinagesic® Capsules decreased steadily from 2001 to 2006. The decrease in prevalence might me due to the increased availability of more cost-effective combination analgesics.

Meprobamate is a specified schedule 5 active ingredient, therefore is controlled by strict regulations. Specified schedule 5 substances are subject to additional control in terms of section 22A of the Medicines and Related Substances Act as required under the provisions of the 1971 Convention on Psychotropic Substances (S.A. 2003). The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Synaleve® Capsules and Trinagesic® Capsules.

The average cost for Synaleve® capsules fluctuated between 2001 and 2006 while the average cost for Trinagesic® Capsules decreased dramatically

between 2002 and 2006. Th fluctuation and decrease in average cost may be due to the implementation of the new price structures (Tshabalala-Msimang, 2004:5).

The effect size (d-values) calculated between the average cost per medicine item for Synaleve® Capsules for the period 2001 to 2006 is of no practical significance (d<0.8) while the effect size (d-values) for Trinagesic® capsules for the period 2001 to 2006 is of practical significance (d>0.8).

The CPI for both Synaleve® Capsules and Trinagesic® Capsules was more than one for most of the study periods, giving us an indication that the therapy utilised is quite expensive.

5.3.3.37 Paracetamol 400mg/ Codeine phosphate 8mg/ Caffeine 200mg

According to the database, there were multiple Paracetamol 400mg, Codeine phosphate 8mg and Caffeine 200mg combination analgesic products claimed in 2001, but by 2006 only the innovator Docdol® Tablets was still claimed. The cost and prevalence of these analgesic combination are described in Table 5.48.

Table 5.48 Prevalence and cost of individual medicine items containing Paracetamol 400mg, Codeine phosphate 8mg and Caffeine 200mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Antipyn® Tab (S2)	853	56.51±38.71	48205.18	0.33	0.26	0.78
	Innovator	Docdol® Tab (S2)	631	66.16±18.42	41749.89	0.24	0.22	0.93
	Innovator	Nopyn® Tab (S2)	137	14.64±1.41	2005.55	0.05	0.01	0.21
	Generic	Acugesil® Tab (S2)	48	13.83±7.34	663.61	0.02	0.00	0.18
	Generic	Dynapayne® Tab (S2)	4	12.25±2.43	49.01	0.00	0.00	0.00
	Generic	Maxadol Forte® Tab (S2)	4	26.51±16.74	106.05	0.00	0.00	0.00
	Generic	Painrite Fort® Cap (S2)	143	55.18±29.08	7891.26	0.05	0.04	0.84
2002	Innovator	Antipyn® Tab (S2)	593	72.00±40.00	42696.98	0.19	0.17	0.91
	Innovator	Docdol® Tab (S2)	690	78.97±24.10	54491.54	0.22	0.22	1.00
	Generic	Maxadol Forte® Tab (S2)	2	13.25±4.36	26.50	0.00	0.00	0.00
	Generic	Painrite Fort® Cap (S2)	148	35.90±12.15	7891.61	0.05	0.03	0.64
2004	Innovator	Antipyn® Tab (S2)	84	71.57±34.94	6012.24	0.02	0.03	1.41
	Innovator	Docdol® Tab (S2)	362	68.46±28.81	24782.26	0.09	0.12	1.29
	Generic	Dynapayne® Tab (S2)	2	19.67±11.69	39.33	0.00	0.00	0.00
	Generic	Painrite Fort® Tab (S2)	3	55.59±39.83	166.78	0.00	0.00	0.00
2005	Innovator	Antipyn® Tab (S2)	8	49.49±10.39	395.91	0.00	0.00	0.00
	Innovator	Docdol® Tab (S2)	129	59.70±21.46	7701.56	0.05	0.05	1.08
2006	Innovator	Docdol® Tab (S2)	33	52.08±20.21	1718.48	0.02	0.02	0.98

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The number of combination analgesic agents containing Paracetamol 400mg, Codeine phosphate 8mg and Caffeine 200mg decreased from seven different innovator and generic brand names available in 2001, to only one, namely Docdol® tablets, available in 2006. The prevalence of all Paracetamol 400mg, Codeine phosphate 8mg and Caffeine 200mg analgesic combinations decreased from 2001 to 2006. The decrease in prevalence might me due to an increased availability of other combination analgesics.

The after an increase from 2001 to 2002, the average cost of Antipyn® tablets and Docdol® tablets decreased dramatically from 2002 to 2005, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). The effect size (d-values) calculated between the average cost per medicine item for all combination analgesic agents containing Paracetamol 400mg, Codeine phosphate 8mg and Caffeine 200mg for the period 2001 to 2006 is of no practical significance (d<0.8).

Antipyn® tablets and Docdol® tablets had CPI's >1 for certain study years, indicating that both the products were relatively expensive.

5.3.3.38 Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg

According to the database, there was only one Paracetamol 500mg, Codeine phosphate 10mg and Meprobamate 125mg innovator combination analgesic product, Meprogesic® Tablets, claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.49.

Table 5.49 Prevalence and cost of individual medicine items containing Paracetamol 500mg, Codeine phosphate 10mg and Meprobamate 125mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Tradename®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Meprogesic® Tab (S5)	177	25.24±15.58	4466.92	0.07	0.02	0.34
2002	Innovator	Meprogesic® Tab (S5)	241	28.28±16.60	6814.54	0.08	0.03	0.35
2004	Innovator	Meprogesic® Tab (S5)	520	19.95±11.56	10372.39	0.14	0.05	0.35
2005	Innovator	Meprogesic® Tab (S5)	449	14.94±6.27	6706.43	0.16	0.05	0.29
2006	Innovator	Meprogesic® Tab (S5)	120	17.63±8.97	2116.15	0.06	0.02	0.40

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

Meprobamate is a specified schedule 5 active ingredient, therefore is controlled by strict regulations. Specified schedule 5 substances are subject to additional control in terms of section 22A of the Medicines and Related Substances Act as required under the provisions of the 1971 Convention on Psychotropic Substances (S.A. 2003).

The prevalence of Meprogesic® tablets increased steadily from 2001 to 2005 after which a decrease was seen between 2005 and 2006. The increase in prevalence might me due to the fact that Meprogesic® tablets is more cost-effective than other combination analgesics.

The after an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2005, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). The effect size (d-values) calculated between the average cost per medicine item for Meprogesic® tablets for the period 2001 to 2006 is of no practical significance (d<0.8).

The CPI is <1 for the entire study period, giving us an indication that the therapy utilised is note very expensive.

5.3.3.39 Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg

The results in Table 5.50 reveal that there was only one Propoxyphene HCl 65mg, Aspirin 375mg and caffeine 30mg innovator combination analgesic product, Doloxene Co-65® Capsules, claimed The cost and prevalence of the analgesic combination is described in Table 5.50.

Table 4.50 Prevalence and cost of individual medicine items containing Propoxyphene HCl 65mg, Aspirin 375mg and caffeine 30mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Doloxene Co-65® Cap (S5)	1371	202.37±141.56	277448.44	0.52	1.48	2.84
2002	Innovator	Doloxene Co-65® Cap (S5)	1173	252.90±188.98	296649.50	0.37	1.20	3.25
2004	Innovator	Doloxene Co-65® Cap (S5)	944	153.72±114.24	145112.83	0.25	0.68	2.73
2005	Innovator	Doloxene Co-65® Cap (S5)	472	158.79±116.06	74950.41	0.17	0.53	3.09
2006	Innovator	Doloxene Co-65® Cap (S5)	367	159.81±103.43	58651.57	0.20	0.67	3.34

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Doloxene Co-65® Capsules decreased steadily from 2001 to 2005 after which an increase was seen from 2005 to 2006. Doloxene Co-65® Capsules represented 0.52% of all combination analgesic medicine items on the total database in 2001, but only 0.17% and 0.20% in 2005 and 2006

respectively. The decrease in prevalence might be due to the increased availability of more cost-effective combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Doloxene Co-65® Capsules.

After an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). Between 2004 and 2006 the average cost for Doloxene Co-65® Capsules increased.

The effect size (d-values) calculated between the average cost per medicine item for Doloxene Co-65® Capsules for the period 2001 to 2006 is of no practical significance (d<0.8). The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.40 Propoxyphene HCl 50mg/ Paracetamol 323mg

According to the database, there was only one Propoxyphene HCl 50mg and Paracetamol 323mg innovator combination analgesic product, Distalgesic® Tablets, claimed from 2001. The cost and prevalence of this analgesic combination is described in Table 5.51.

Table 4.51 Prevalence and cost of individual medicine items containing Propoxyphene HCl 50mg and Paracetamol 323mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Distalgesic® Tab (S5)	1200	115.14±58.88	138165.83	0.46	0.73	1.60
2002	Innovator	Distalgesic® Tab (S5)	393	157.76±95.53	62000.21	0.12	0.25	2.10
2004	Innovator	Distalgesic® Tab (S5)	557	93.45±65.15	52050.90	0.15	0.24	1.63
2005	Innovator	Distalgesic® Tab (S5)	341	69.97±30.10	23861.46	0.12	0.17	1.39
2006	Innovator	Distalgesic® Tab (S5)	128	81.16±50.90	10388.89	0.07	0.12	1.69

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Distalgesic® tablets decreased steadily from 2001 to 2006. Distalgesic® tablets represented 0.46% of all combination analgesic medicine items on the total database in 2001, but only 0.07% in 2006. The decrease in prevalence might be due to the increased availability of more cost-effective combination analgesics. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Distalgesic® tablets.

After an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). The effect size (d-values) calculated between the average cost per medicine item for Distalgesic® tablets for the period 2001 to 2006 is of no practical significance (d<0.8). The average cost for Distalgesic® tablets increased between 2005 and 2006, probably due to the changes in the pricing structure in 2006 (Tshabalala-Msimang, 2006).

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.41 Propoxyphene HCl 50mg/ Paracetamol 250mg

There was only one Propoxyphene HCl 50mg and Paracetamol 250mg combination analgesic product, Doxyfene® Capsules, available on the Interpharm® database from 2001. The cost and prevalence of this analgesic combination is described in Table 5.52.

Table 5.52 Prevalence and cost of individual medicine items containing Propoxyphene HCl 50mg and Paracetamol 250mg for the period 2001, 2002, 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2001	Innovator	Doxyfene® Cap (S5)	3041	156.13±89.75	474805.34	1.16	2.53	2.18
2002	Innovator	Doxyfene® Cap (S5)	3197	181.83±133.30	581323.62	1.01	2.36	2.33
2004	Innovator	Doxyfene® Cap (S5)	3740	153.79±121.61	575156.80	0.98	2.70	2.76
2005	Innovator	Doxyfene® Cap (S5)	1382	139.11±104.57	192248.80	0.49	1.35	2.75
2006	Innovator	Doxyfene® Cap (S5)	318	148.13±109.06	47106.65	0.17	0.54	3.15

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Doxyfene® capsules decreased steadily from 2001 to 2006. Doxyfene® capsules represented 1.16% of all combination analgesic medicine items on the total database in 2001, but only 1.17% in 2006. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of Doxyfene® capsules.

After an increase from 2001 to 2002, the average cost per medicine item decreased dramatically from 2002 to 2004, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). The effect size (d-values) calculated between the average cost per

medicine item for Doxyfene® capsules for the period 2001 to 2006 is of no practical significance (d<0.8).

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.3.42 Paracetamol 325mg/ Tramadol 37.5mg

The results in Table 5.53 reveal that there was only one Paracetamol 325mg and Tramadol 37.5mg innovator combination analgesic product, Tramacet® Tablets, claimed from 2004 to 2006. The cost and prevalence of this analgesic combination is described in Table 5.53.

Table 5.53 Prevalence and cost of individual medicine items containing Paracetamol 325mg and Tramadol 37.5mg for the period 2004, 2005 and 2006.

Period	Innovator/ Generic	Combination analgesic agent (Trade name®)	Prevalence	Average cost (R)	Total cost (R)	Prevalence %*	Cost %@	CPI
2004	Innovator	Tramacet® Tab (S5)	6789	70.97±47.02	481810.76	1.78	2.26	1.27
2005	Innovator	Tramacet® Tab (S5)	5792	66.77±54.42	386725.00	2.06	2.71	1.32
2006	Innovator	Tramacet® Tab (S5)	6081	76.96±68.96	467994.44	3.24	5.32	1.64

%* The prevalence of the individual combination analgesic medicine item divided by the prevalence of the total number of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

%@ The total cost of the individual combination analgesic medicine item divided by the total cost of all combination analgesic medicine items for the corresponding study period, multiplied by a hundred.

The prevalence of Tramacet® tablets increased steadily from 2004 to 2006. Tramacet® tablets represented 1.78% of all combination analgesic medicine items on the total database in 2004 and increased to 3.24% in 2006.

The average cost per medicine item decreased from 2004 to 2005, probably due to the implementation of the new price structure in 2004 (Tshabalala-Msimang, 2004:5). The effect size (d-values) calculated between the average cost per medicine item for Tramacet® tablets for the period 2004 to 2006 is of no practical significance (d<0.8).

The CPI is > 1 for the entire study period, giving us an indication that the therapy utilised is very expensive.

5.3.4 Average number of prescriptions per patient per year

Table 5.54 summarises the number of patients receiving prescriptions and the number of prescriptions per patient per year.

Table 5.54 Average number of prescriptions per patient per year

	2001	2002	2004	2005	2006
Total number of patients on the database	337003	490198	657009	379352	264272
Number of patients receiving **combination analgesic** prescriptions	135505	170860	231147	154605	104304
% patients receiving **combination analgesic** prescriptions	40.21	34.86	35.18	40.76	39.47
Total number of prescriptions on the database (containing any medicine item(s))	1473512	2072945	2591604	1616262	993467
Number of **combination analgesic** prescriptions on the database	258537	313751	376507	277068	184729
% number of **combination analgesic** prescriptions on the database	17.55	15.14	14.53	17.14	18.59
Number of prescriptions per patient per year (containing any medicine item(s))	4.37±4.45	4.23±4.52	3.94±4.27	4.26±4.87	3.76±4.56
Number of **combination analgesic** prescriptions per patient per year	1.91±1.73	1.84±1.64	1.63±1.34	1.79±1.65	1.77±1.65

The ***number of prescriptions per patient per year*** decreased from 4.37±4.45 in 2001 to 3.94±4.27 in 2004 after which it increased to 4.26±4.87 in 2005. From 2005 to 2006 the average number of prescriptions per patient decreased from 4.26±4.87 to 3.76±4.56. The ***number of combination analgesic prescriptions per patient per year*** decreased from 1.91±1.73 in 2001 to 1.63±1.34 in 2004 after which it increased to 1.79±1.65 in 2005. From 2005 to 2006, there was a slight decrease to 1.77±1.65 combination analgesic prescriptions per patient per year.

The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in combination analgesic prescriptions per patient per year between 2002 and 2004.

5.4 Prevalence and cost of combinations of analgesic medicine items

The average cost, standard deviation and prevalence of analgesics prescribed as combination therapy for the years 2004, 2005 and 2006 is summarised in Appendix A-E. For the analysis of analgesics prescribed as combination therapy, all analgesics classified in group 3 according to the MIMS® classification system were included.

The prevalence and cost percentages of analgesic combination therapy is summarised in Table 5.55 and 5.56.

Table 5.55 Prevalence of combination therapy of analgesics

	2004		2005		2006	
	Number	**%**	**Number**	**%**	**Number**	**%**
Number of prescriptions containing one analgesic in mono-therapy (n)	452965	97.37	332059	97.21	223746	97.29
Number of prescriptions containing two analgesics in double-combination therapy (n)	11953	2.57	9322	2.73	6027	2.62
Number of prescriptions containing three analgesics in triple-combination therapy (n)	262	0.06	198	0.06	145	0.06
Number of prescriptions containing four analgesics in combination therapy (n)	12	0.00	6	0.00	10	0.00
Number of prescriptions containing five analgesics in combination therapy (n)			1	0.00	2	0.00
Total number of prescriptions containing at least one analgesic medicine item (N)	**465193**	**100.00**	**341591**	**100.00**	**229980**	**99.98**

Table 5.56 Cost of combination therapy of analgesics

	2004		2005		2006	
	Cost (R)	**%**	**Cost (R)**	**%**	**Cost (R)**	**%**
Total cost of analgesics in mono-therapy (R)	23593107.6	93.81	15712953.41	93.43	9869250.05	92.79
Total cost of analgesics in double combination therapy (R)	1462378.81	5.81	1051847.56	6.25	721596.31	6.78
Total cost of analgesics in triple combination therapy (R)	68209.48	0.27	28112.29	0.17	24165.74	0.23
Total cost of analgesics in four analgesic combinations (R)	10302.83	0	1506.18	0.01	2779.44	0.03
Total cost of analgesics in five analgesics combination (R)			1239.42	0.01	198.93	0.00
Total cost of analgesic prescriptions (R) (N)	**25149035.88**	**99.90**	**16818074.72**	**99.87**	**10636313.51**	**99.83**

The prevalence and cost percentages of analgesic combination therapy is summarised in Table 5.55 and 5.56 is discussed in sections 5.4.1 to 5.4.3.

5.4.1 Prevalence and cost of analgesics that occurred as mono-therapy

The average cost, standard deviation and prevalence of analgesics prescribed as mono-therapy were analysed for the different study years namely 2004, 2005 and 2006 (see appendix A1-3).

A total sum of 452 965 prescriptions for mono-therapy of analgesics occurred with a total cost amounting to R23 593 107.60 in 2004. Thus, 97.37% (N=465 193) of the analgesic containing prescriptions prescribed during 2004 were cases where analgesics were prescribed as mono-therapy representing

93.81% (N=R25 149 035.88) of the total cost of analgesics (refer to table 5.55 and 5.56).

A total sum of 332 059 prescriptions for mono-therapy of analgesics occurred with a total cost amounting to R15 712 953.41 in 2005. Thus, 97.21% (N=341 591) of the analgesic containing prescriptions prescribed during 2005 were cases where analgesics were prescribed as mono-therapy representing 93.43% (N=16 818 074.72) of the total cost of analgesics (refer to table 5.55 and 5.56).

A total sum of 223 746 prescriptions for mono-therapy of analgesics occurred with a total cost amounting to R9 869 250.05 in 2006 Thus, 97.29% (N=229 980) of the analgesic containing prescriptions prescribed during 2006 were cases where analgesics were prescribed as mono-therapy representing 92.79% (N=R10 636 313.51) of the total cost of analgesics (refer to table 5.55 and 5.56).

A possible explanation for the high percentage of analgesics prescribed as mono-therapy, might be the fact that 76.73% (n=347566), 80.99% (n=268927) and 80.19% (n=179420) of all analgesic mono-therapies for the respective years 2004, 2005 and 2006 was for combination analgesics, which already contain more than one analgesic active ingredient.

It is clear that both the prevalence and cost percentages of analgesic mono-therapy stayed relatively constant from 2004 to 2006.

Due to the large number of prescriptions containing a single analgesic agent only the top ten most frequently prescribed mono-therapies will be analysed further. Table 5.57, 5.58 and 5.59 represents the top ten most frequently prescribed analgesics that were utilised as mono-therapy only for the years 2004, 2005 and 2006, with an indication of the number of prescriptions containing the different analgesic mono-therapies, the cost of the mono-therapies, the average cost, standard deviation, the cost and prevalence percentages as well as the cost-prevalence index values.

Table 5.57 Prevalence, cost and CPI values of analgesics utilised as mono-therapy for the year 2004.

	Agents in monotherapy	Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	99 540	21.98	64.45±27.58	6415324.62	27.19	1.24
2	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	56 748	12.53	23.83±32.23	1352238.21	5.73	0.46
3	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	48 692	10.75	48.67±20.16	2370076.39	10.05	0.93
4	Paracetamol	32 526	7.18	14.61±15.03	475146.62	2.01	0.28
5	Mefenamic acid	32 025	7.07	28.59±27.27	915599.78	3.88	0.55
6	Ibuprofen 200mg/Paracetamol 250mg	29 625	6.54	54.69±21.09	1620189.96	6.87	1.05
7	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	26 205	5.79	38.28±34.25	1003224.75	4.25	0.74
8	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	20 093	4.44	21.87±15.08	439336.77	1.86	0.42
9	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	17 460	3.85	129.52±86.37	2261342.51	9.58	2.49
10	Aspirin	11 612	2.56	11.32±7.85	131480.57	0.56	0.22
	TOTAL	**374526**	**82.68**		**16983960.18**	**71.99**	**0.87**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=452 965) for all mono-therapies was used to calculate the prevalence percentage and the total cost (n=R23 593 107.60) of all mono-therapies was used to calculate percentages.

It can be concluded from table 5.57 that seven out of the top-ten most frequently prescribed analgesic mono-therapies prescribed in 2004 were combination analgesics. The combination of ibuprofen 200mg, paracetamol 250mg and codeine 10mg (Myprodol® capsules and Myprodol® suspension) had the highest prevalence (n=99 540) representing 21.98% of all analgesic mono-therapies with a cost of R6 415 324.62, followed by the combination of paracetamol 320mg, codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg (e.g. Stillpane®, Stopayne®, Paynagon®, Salterpyn® etc.) with a prevalence of 56 748, representing 12.53% of all analgesic mono-therapies and a total cost of R1 352 238.21. The combination of ibuprofen 200mg, paracetamol 350mg and codeine 10mg (Mybulen® tablets) had the third highest prevalence (n=48 692), representing 10.75% of all analgesic mono-therapies and a total cost of R2 370 076.39 during 2004 (refer to figure 5.4).

When comparing the average costs of the top ten analgesics most frequently prescribed as mono-therapy for 2004, depicted in table 5.57, it is clear that the combination of paracetamol 500mg, dextropopoxyphene 50mg, diphenhydramine HC 5mg and caffeine 50mg had the highest average cost (R129.52±86.37), the combination of ibuprofen 200mg, paracetamol 250mg

and codeine 10mg (Myprodol® capsules and Myprodol® suspension) had the second largest average cost (R64.45±27.58) and the combination of ibuprofen 200mg and paracetamol 250mg (Lotum® suspension and Mypaid® capsules) had the third highest average cost (R54.69±21.09).

Table 5.58 Prevalence, cost and CPI values of analgesics utilised as mono-therapy for the year 2005.

	Agents in monotherapy	Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	83 609	25.18	61.23±26.95	5119199.14	32.58	1.29
2	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	42 721	12.87	48.38±19.05	2066727.02	13.15	1.02
3	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	34 259	10.32	19.41±23.46	664849.31	4.23	0.41
4	Paracetamol	25 814	7.77	11.9±13.99	307310.84	1.96	0.25
5	Mefenamic acid	25 238	7.60	23.33±19.48	588850.68	3.75	0.49
6	Ibuprofen 200mg/Paracetamol 250mg	23 601	7.11	44.05±23.02	1039739.14	6.62	0.93
7	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	17 166	5.17	27.56±24.13	473107.54	3.01	0.58
8	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	12 691	3.82	15.53±10.42	197173.26	1.25	0.33
9	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	10 166	3.06	116.18±69.87	1181094.62	7.52	2.46
10	Orphenadrine 35mg/Paracetamol 450mg	8 690	2.62	34.09±14.29	296253.64	1.89	0.72
	TOTAL	**283 955**	**85.51**		**11934305.19**	**75.95**	**0.89**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=332 059) for all mono-therapies was used to calculate the prevalence percentage and the total cost (n=R15 712 953.41) of all mono-therapies was used to calculate percentages.

It can be concluded from table 5.58 that eight out of the top-ten most frequently prescribed analgesic mono-therapies prescribed in 2005 were combination analgesics. The combination of ibuprofen 200mg, paracetamol 250mg and codeine 10mg (e.g. Mybulen® suspension, Myprodol® capsules, Mybulen® capsules, Gen-payne®, Ibupain Forte® etc.) had the highest prevalence (n=83 609) representing 25.18% of all analgesic mono-therapies with a cost of R5 119 199.14, followed by the combination of ibuprofen 200mg, paracetamol 350mg and codeine 10mg (Mybulen® tablets) with a prevalence of 42 721, representing 12.87% of all analgesic mono-therapies and a total cost of R2066727.02. The combination of paracetamol 320mg, codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg (e.g. Stillpane®, Stopayne®, Paynagon®, Salterpyn® etc.) had the third highest prevalence (n=34 259) representing 10.32% and a total cost of R664 849.31 during 2005 (refer to figure 5.4).

When comparing the average costs of the top ten analgesics most frequently prescribed as mono-therapy for 2005, depicted in table 5.58, it is clear that the combination of paracetamol 500mg, dextropopoxyphene 50mg, diphenhydramine HC 5mg and caffeine 50mg had the highest average cost (R116.18±69.87), the combination of ibuprofen 200mg, paracetamol 250mg and codeine 10mg (e.g. Mybulen® suspension, Myprodol® capsules, Mybulen® capsules, Gen-payne®, Ibupain Forte® etc.) had the second largest average cost (R61.23±26.95) and the combination of ibuprofen 200mg, paracetamol 350mg and codeine 10mg (Mybulen® tablets) had the third highest average cost (R48.38±19.05).

Table 5.59 Prevalence, cost and CPI values of analgesics utilised as mono-therapy for the year 2006.

	Agents in monotherapy	Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	60 556	27.06	47.73±17.09	2890093.08	29.28	1.08
2	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	31 067	13.88	54.72±31.42	1699943.77	17.22	1.24
3	Paracetamol	19 295	8.62	13.06±31.69	251975.01	2.55	0.30
4	Mefenamic acid	19 096	8.53	21.99±17.80	420020.31	4.26	0.50
5	Ibuprofen 200mg/Paracetamol 250mg	18 965	8.48	23.81±25.85	451467.51	4.57	0.54
6	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	17 023	7.61	24.06±28.80	409631.00	4.15	0.55
7	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	13 906	6.22	31.36±25.82	436096.49	4.42	0.71
8	Orphenadrine 35mg/Paracetamol 450mg	6 965	3.11	34.12±13.05	237572.24	2.41	0.77
9	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6 915	3.09	15.17±8.06	104867.75	1.06	0.34
10	Paracetamol 325mg/Tramadol HCL 37.5mg	5 775	2.58	77.02±68.96	444765.26	4.51	1.75
	TOTAL	**199 563**	**89.19**		**7346432.42**	**74.44**	**0.83**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=223 746) for all mono-therapies was used to calculate the prevalence percentage and the total cost (n=R9 869 250.05) of all mono-therapies was used to calculate percentages.

It can be concluded from table 5.59 that eight out of the top-ten most frequently prescribed analgesic mono-therapies prescribed in 2006 were combination analgesics. The combination of ibuprofen 200mg, paracetamol 250mg and codeine 10mg (e.g. Mybulen® suspension, Myprodol® capsules, Mybulen® capsules, Gen-payne®, Ibupain Forte® etc.) had the highest prevalence (n=60 556), representing 27.06% of all analgesic mono-therapies with a cost of R2 890 093.08, followed by the combination of ibuprofen 200mg, paracetamol 350mg and codeine 10mg (Mybulen® tablets) with a prevalence of 31 067, representing 13.88% of all analgesic mono-therapies and a total cost of R1699943.77. The combination of paracetamol 320mg,

codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg (e.g. Stillpane®, Stopayne®, Paynagon®, Salterpyn® etc.) had the sixth highest prevalence (n=17 023) representing only 7.61% of all analgesic mono-therapies and a total cost of R409631.00 during 2006 (refer to figure 5.4).

When comparing the average costs of the top ten analgesics most frequently prescribed as mono-therapy for 2006, depicted in table 5.59, it is clear that the combination of Paracetamol 325mg/Tramadol HCL 37.5mg (Tramacet® tablets) had the highest average cost (R77.02±68.96), the combination of ibuprofen 200mg, paracetamol 350mg and codeine 10mg (Mybulen® tablets) had the second highest average cost (R54.72±31.42) and the combination of ibuprofen 200mg, paracetamol 250mg and codeine 10mg (e.g. Mybulen® suspension, Myprodol® capsules, Mybulen® capsules, Gen-payne®, Ibupain Forte® etc.) had the third largest average cost (R47.73±17.09).

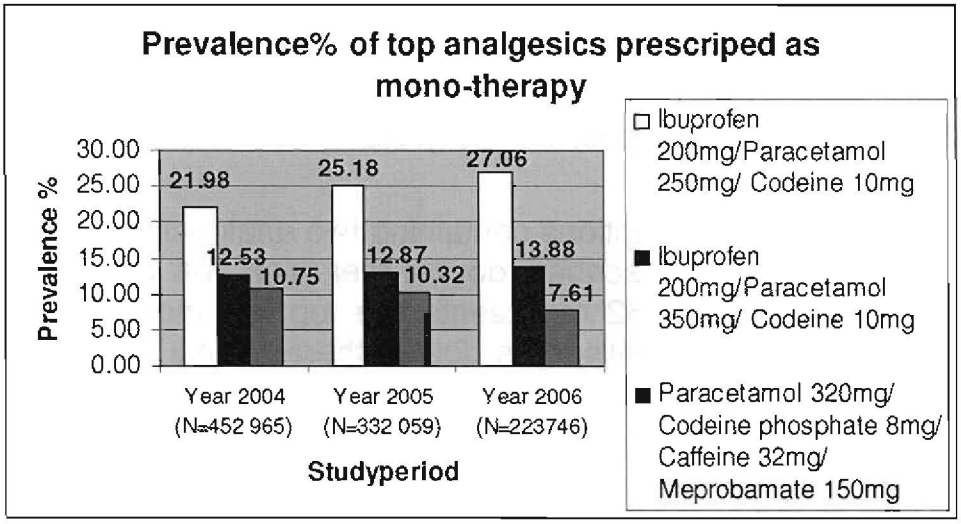

Figure 5.4 Prevalence percentage of top analgesics prescribed as mono-therapy.

The prevalence of both the Ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination and the ibuprofen 200mg, paracetamol 350mg and codeine 10mg combination as mono-therapy increased from 2004 to 2006, while the prevalence of the paracetamol 320mg, codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg combination decreased from 2004 to 2006. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in prevalence of the specified schedule 5 meprobamate containing combination.

5.4.2 Prevalence and cost of analgesics that occurred as double-therapy

The average cost, standard deviation and prevalence of analgesics prescribed as double-therapy were analysed for the different study years namely 2004, 2005 and 2006 (see appendix B1-3).

A total sum of 11 953 prescriptions for double-therapy of analgesics occurred with a total cost amounting to R1 462 378.81 in 2004. Thus, 2.57% (N=465 193) of the analgesic containing prescriptions prescribed during 2004 were cases where analgesics were prescribed as double-therapy representing 5.81% (N=R25 149 035.88) of the total cost of analgesics (refer to table 5.55 and 5.56).

A total sum of 9 322 prescriptions for double-therapy of analgesics occurred with a total cost amounting to R1051847.56 in 2005. Thus, 2.73% (N=341 591) of the analgesic containing prescriptions prescribed during 2005 were cases where analgesics were prescribed as double-therapy representing 6.25% (N=16 818 074.72) of the total cost of analgesics (refer to table 5.55 and 5.56).

A total sum of 6027 prescriptions for double-therapy of analgesics occurred with a total cost amounting to R721 596.31 in 2006 Thus, 2.62% (N=229 980) of the analgesic containing prescriptions prescribed during 2006 were cases where analgesics were prescribed as double-therapy representing 6.78% (N=R10 636 313.51) of the total cost of analgesics (refer to table 5.55 and 5.56).

Due to the large number of prescriptions containing two analgesic agents only the top ten most frequently prescribed double-therapies will be analysed further. Table 5.60, 5.61 and 5.62 represents the top ten most frequently prescribed analgesics that were utilised as double-therapy only for the years 2004, 2005 and 2006, with an indication of the number of prescriptions containing the different analgesic double-therapies, the cost of the double-therapies, the average cost, standard deviation, the cost and prevalence percentages as well as the cost-prevalence index values.

Table 5.60 Prevalence, cost and CPI values of analgesics utilised as double-combination therapy for the year 2004.

	Agents in double combination therapy		Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost%	CPI
1	Mefenamic acid	Paracetamol	969	8.11	57.32± 34.97	55547.86	3.80	0.47
2	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	673	5.63	52.45± 32.39	35302.13	2.41	0.43
3	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	464	3.88	102.94± 61.63	47765.05	3.27	0.84
4	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Tramadol	320	2.68	290.08± 221.62	92824.14	6.35	2.37
5	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	291	2.43	199.07± 98.43	75930.40	5.19	2.13
6	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	269	2.25	55.45± 30.67	14914.84	1.02	0.45
7	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	261	2.18	68.60± 36.73	17904.71	1.22	0.56
8	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	258	2.16	102.06± 65.65	26331.44	1.80	0.83
9	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Tramadol	252	2.11	145.22± 150.23	36596.12	2.50	1.19
10	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	243	2.03	99.54± 36.61	24188.22	1.65	0.81
	TOTAL		**4000**	**33.46**		**427304.91**	**29.22**	**0.87**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=11 953) for all double-therapies was used to calculate the prevalence percentage and the total cost (n=R1 462 378.8) of all double-therapies was used to calculate percentages

It can be concluded from table 5.60 that nine out of the top-ten most frequently prescribed analgesic double-therapies prescribed in 2004 contained at least one combination analgesic. Five out of the ten most frequently prescribed analgesic double-therapies prescribed contained two combination analgesics.

When comparing the average costs of the top ten analgesics most frequently prescribed as double-therapy for 2004, depicted in table 5.60, it is clear that the combination of the ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination with tramadol, had the highest average cost (R290.08± 221.62).

Table 5.61 Prevalence, cost and CPI values of analgesics utilised as double-combination therapy for the year 2005.

	Agents in double combination therapy		Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost%	CPI
1	Mefenamic acid	Paracetamol	735	7.88	51.49± 27.54	37845.6	3.60	0.46
2	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	353	3.79	44.24± 23.41	15617.43	1.48	0.39
3	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Tramadol	349	3.74	283.69± 189.81	99006.15	9.41	2.51
4	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	342	3.67	93.39± 49.32	31598.65	3.00	0.82
5	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	318	3.41	72.48± 17.72	23048.49	2.19	0.64
6	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	274	2.94	93.04± 35.41	25493.46	2.42	0.82
7	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	217	2.33	89.07± 43.69	19327.31	1.84	0.79
8	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	215	2.31	61.37± 26.67	13195.32	1.25	0.54
9	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Mefenamic acid	201	2.16	93.60± 33.08	18813.24	1.79	0.83
10	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol	189	2.03	89.49± 33.79	16914.01	1.61	0.79
	TOTAL		**3193.00**	**34.25**		**300859.66**	**28.60**	**0.84**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=9 322) for all double-therapies was used to calculate the prevalence percentage and the total cost (n=R1 051 847.56) of all double-therapies was used to calculate percentages.

It can be concluded from table 5.61 that nine out of the top-ten most frequently prescribed analgesic double-therapies prescribed in 2005 contained at least one combination analgesic. Five out of the ten most frequently prescribed analgesic double-therapies prescribed contained two combination analgesics.

When comparing the average costs of the top ten analgesics most frequently prescribed as double-therapy for 2005, depicted in table 5.61, it is clear that

the combination of the ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination with tramadol, had the highest average cost (R283.69± 189.81).

Table 5.62 Prevalence, cost and CPI values of analgesics utilised as double-combination therapy for the year 2006.

	Agents in double combination therapy		Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Mefenamic acid	Paracetamol	474	7.86	54.04± 26.66	25612.81	3.55	0.45
2	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	283	4.70	82.51± 20.60	23351.65	3.24	0.69
3	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Tramadol	265	4.40	234.62± 170.57	62173.74	8.62	1.96
4	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	252	4.18	72.43± 22.52	18253.29	2.53	0.60
5	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 325mg/Tramadol HCL 37.5mg	194	3.22	254.83± 178.24	49437.69	6.85	2.13
6	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	173	2.87	40.16± 16.57	6947.35	0.96	0.34
7	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	167	2.77	75.14± 29.26	12548.15	1.74	0.63
8	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	155	2.57	64.96± 25.67	10069.53	1.40	0.54
9	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	141	2.34	75.38± 39.67	10628.18	1.47	0.63
10	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol	121	2.01	80.72± 54.99	9766.74	1.35	0.67
	TOTAL		**2225**	**36.92**		**228789.13**	**31.71**	**0.86**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=6 027) for all double-therapies was used to calculate the prevalence percentage and the total cost (n=R721 596.31) of all double-therapies was used to calculate percentages.

It can be concluded from table 5.62 that nine out of the top-ten most frequently prescribed analgesic double-therapies prescribed in 2006 contained at least one combination analgesic. Six out of the ten most frequently prescribed analgesic double-therapies prescribed contained two combination analgesics.

When comparing the average costs of the top ten analgesics most frequently prescribed as double-therapy for 2006, depicted in table 5.62, it is clear that the combination of the ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination with the paracetamol 325mg and tramadol HCL 37.5mg combination had the highest average cost (R254.83± 178.24). The combination of the ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination with tramadol, had the second highest average cost (R234.62± 170.57).

5.4.3 Prevalence and cost of analgesics that occurred as triple-therapy

The average cost, standard deviation and prevalence of analgesics prescribed as triple-therapy were analysed for the different study years namely 2004, 2005 and 2006 (see appendix C1-3).

A total sum of 262 prescriptions for triple-therapy of analgesics occurred with a total cost amounting to R68 209.48 in 2004. Thus, 0.06% (N=465 193) of the analgesic containing prescriptions prescribed during 2004 were cases where analgesics were prescribed as triple-therapy representing 0.27% (N=R25 149 035.88) of the total cost of analgesics (refer to table 5.55 and 5.56).

In 2005, a total of 198 prescriptions for triple-therapy of analgesics occurred with a total cost amounting to R28 112.29. Therefore, during 2005 0.06% (N=341 591) of prescriptions which contained analgesics were cases where analgesics were prescribed as triple-therapy, representing 0.13% (N=16 818 074.72) of the total cost of analgesics (refer to table 5.55 and 5.56).

A total number of 145 prescriptions for triple-therapy of analgesics occurred with a total cost amounting to R24 165.74 in 2006. Thus, during 2006 0.06% (N=229 980) of the prescriptions which contained analgesics were cases where analgesics were prescribed as triple-therapy representing 0.23% (N=R10 636 313.51) of the total cost of analgesics (refer to table 5.55 and 5.56).

Due to the number of prescriptions containing three analgesic agents only the most frequently prescribed triple-therapies will be analysed further. Table 5.63, 5.64 and 5.65 represents the most frequently prescribed analgesics that

were utilised as triple-therapy only for the years 2004, 2005 and 2006, with an indication of the number of prescriptions containing the different analgesic triple-therapies, the cost of the triple-therapies, the average cost, standard deviation, the cost and prevalence percentages as well as the cost-prevalence index values.

Table 5.63 Prevalence, cost and CPI values of analgesics utilised as triple-combination therapy for the year 2004.

	Agents in triple-combination therapy			Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Mefenamic acid	Paracetamol	Paracetamol	10	3.82	105.09± 53.94	1050.89	1.54	0.4
2	Mefenamic acid	Mefenamic acid	Paracetamol	9	3.44	95.78± 49.90	862.04	1.26	0.37
3	Mefenamic acid	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Tramadol	8	3.05	220.97± 31.75	1767.78	2.59	0.85
3	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	8	3.05	102.41± 52.41	817.98	1.20	0.39
4	Ibuprofen 200mg/Paracetamol 250mg	Mefenamic acid	Paracetamol	6	2.29	132.30± 63.87	793.79	1.16	0.51
5	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Mefenamic acid	Paracetamol	5	1.91	123.86± 57.83	619.29	0.91	0.48
6	Ibuprofen 200mg/Paracetamol 250mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	1.53	96.61± 14.14	386.44	0.57	0.37
6	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	4	1.53	216.75± 191.19	866.99	1.27	0.83
6	Mefenamic acid	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	4	1.53	86.81± 13.32	347.24	0.51	0.33
TOTAL				**58**	**22.14**		**7512.44**	**11.01**	**0.5**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=262) for all triple-therapies was used to calculate the prevalence percentage and the total cost (n=R68 209.48) of all triple-therapies was used to calculate percentages.

Table 5.64 Prevalence, cost and CPI values of analgesics utilised as triple-combination therapy for the year 2005.

	Agents in triple-combination therapy			Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	7	3.54	78.31± 38.93	548.20	1.95	0.55
2	Aspirin	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	5	2.53	79.49± 14.55	397.45	1.414	0.56
2	Ibuprofen 200mg/Paracetamol 250mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	2.53	111.63± 38.96	558.18	1.986	0.79
3	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Tramadol	4	2.02	602.87± 6.38	2411.48	8.578	4.25
TOTAL				**21**	**10.61**		**3915.31**	**13.93**	**1.31**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=198) for all triple-therapies was used to calculate the prevalence percentage and the total cost (n=R28 112.29) of all triple-therapies was used to calculate percentages.

Table 5.65 Prevalence, cost and CPI values of analgesics utilised as triple-combination therapy for the year 2006.

	Agents in triple-combination therapy			Prevalence	Prevalence %	Average cost (R)	Total cost (R)	Cost %	CPI
1	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	10	6.90	109.27± 0.00	1092.70	4.522	0.66
2	Ibuprofen 200mg/Paracetamol 250mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	3.45	64.51± 29.52	322.53	1.335	0.39
2	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	5	3.45	70.42± 37.79	352.09	1.457	0.42
3	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	2.76	91.77± 10.24	367.08	1.519	0.55
4	Aspirin	Paracetamol	Paracetamol	3	2.07	79.08± 41.33	237.23	0.982	0.47
4	Aspirin	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	2.07	106.43± 26.33	319.28	1.321	0.64
4	Aspirin	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	3	2.07	55.96± 8.80	167.89	0.695	0.34
4	Mefenamic acid	Paracetamol	Paracetamol	3	2.07	71.17± 29.38	213.52	0.884	0.43
TOTAL				**36**	**24.83**		**3072.32**	**12.71**	**0.51**

* The sum of the percentage columns do not add up to a hundred due to the fact that the total number of prescriptions (n=145) for all triple-therapies was used to calculate the prevalence percentage and the total cost (n=R24 165.74) of all triple-therapies was used to calculate percentages.

It can be concluded from table 5.63 that seven out of nine most frequently prescribed analgesic triple therapies prescribed in 2004 contained at least one combination analgesic. One out of the nine most frequently prescribed analgesic triple-therapies prescribed contained three combination analgesics. When comparing the average costs of the analgesics most frequently prescribed as triple-therapy for 2004, depicted in table 5.63, it is clear that the combination of mefenamic acid, tramadol and the paracetamol 320mg, codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg combination had the highest average cost (R220.97± 31.75).

The most frequently prescribed analgesic triple therapies prescribed in 2005 contained at least one combination analgesic (refer to table 5.64.). One out of the four most frequently prescribed analgesic triple-therapies prescribed contained three combination analgesics. The combination of tramadol, the paracetamol 320mg, codeine phosphate 8mg, caffeine 32mg and meprobamate 150mg combination and the dextropropoxyphene HCl 65mg, paracetamol 400mg and L-glutamine 25mg combination had the highest average cost (R602.87± 6.38) (refer to table 5.64.).

It can be concluded from table 5.65 that six out of eight most frequently prescribed analgesic triple therapies prescribed in 2006 contained at least one combination analgesic. Three out of the eight most frequently prescribed analgesic triple-therapies prescribed contained three combination analgesics. When comparing the average costs of the analgesics most frequently prescribed as triple-therapy for 2006, depicted in table 5.65, it is clear that the combination of the ibuprofen 200mg, paracetamol 250mg and codeine 10mg combination, the ibuprofen 200mg, paracetamol 350mg, and codeine 10mg combination and the paracetamol 450mg, doxylamine succinate 5mg, caffeine 450mg and codeine phosphate 10mg combination had the highest average cost (R109.27± 0.00).

5.4.4 Prevalence of combination analgesics that occur as combination therapy

The prevalence of combination analgesics which occur as combination therapy is summarised in table 5.66.

Table 5.66 Prevalence of combination analgesics that occur as combination therapy

One analgesic in mono-therapy	**2004**	**2005**	**2006**
Total number of prescriptions containing one analgesic medicine items (N)	452 965	332 059	223 746
% prescriptions which contain **one** combination analgesic	76.73% (n=347 566)	80.99% (n=268 927)	80.19% (n=179 420)
Two analgesics in combination	**2004**	**2005**	**2006**
Total number of prescriptions containing two analgesic medicine items (N)	11 953	9 322	6 027
% prescriptions containing **one or more** combination analgesic	85.01% (n=10 161)	85.45% (n=7966)	85.35% (n=5144)
% prescriptions which contain **two** combination analgesics	44.27% (n=5 291)	46.19% (n=4 306)	50.80% (n=3 062)
Three analgesics in combination	**2004**	**2005**	**2006**
Total number of prescriptions containing three analgesic medicine items (N)	262	198	145
% prescriptions containing **one or more** combination analgesic	88.55% (n=232)	92.42% (n=183)	92.41% (n=134)
% prescriptions contain **three** combination analgesics	25.95% (n=68)	26.26% (n=52)	37.93% (n=55)
Four analgesics in combination	**2004**	**2005**	**2006**
Total number of prescriptions containing four analgesic medicine items (N)	12	6	10
% prescriptions containing **one or more** combination analgesic	58.33% (n=7)	100.00% (n=6)	100.00% (n=10)
% prescriptions containing **four** combination analgesics	8.33% (n=1)	0.00% (n=0)	40.00% (n=4)
Five analgesics in combination		**2005**	**2006**
Total number of prescriptions containing five analgesic medicine items (N)		1	2
% prescriptions containing **one or more** combination analgesic		100.00% (n=1)	100.00% (n=2)
% prescriptions containing **five** combination analgesics		0.00% (n=0)	50.00% (n=1)

A possible explanation for the high percentage of analgesics prescribed as mono-therapy, might be the fact that 76.73% (n=347566), 80.99% (n=268927) and 80.19% (n=179420) of al analgesic mono-therapies for the respective years 2004, 2005 and 2006 was for combination analgesics, which already contain more than one analgesic active ingredient.

5.5 Prevalence of combination analgesics available without prescription

According to their scheduling status, 27 of the 42 analgesic combinations analysed in this study were available without prescription.

Table 5.67 Number of combination analgesic available without prescription (S0, S1 or S2)

	2001	2002	2004	2005	2006
% Combination analgesics available without a prescription	67.00	84.31	70.80	73.88	79.96
% Combination analgesics only available with a prescription	33.00	15.69	29.20	26.12	20.04
TOTAL	100.00	100.00	100.00	100.00	100.00

The high prescribing rate and use of combination analgesics is a cause for concern, due to the dependence-producing potential of some of the ingredients.

5.6 Chapter summary

In this chapter, the results of the empirical investigation of the prescribing patterns and cost of analgesics, in particular combination analgesics medicine items for the study periods 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, 1 January 2004 to 31 December 2004, 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006 were outlined and conferred.

Chapter 6
Conclusions and recommendations

6.1 Introduction

In this chapter, the conclusions based on the results of the literature review and the empirical investigation, as well as the recommendations derived from the study on the prescribing patterns of combination analgesics will be discussed. The limitations encountered during the study will also be included in this discussion.

6.2 Conclusions

The conclusions and recommendations were based on the specific objectives of the literature study and empirical investigation will be discussed briefly in this section (refer to section 4.2.2).

6.2.1 Conclusions based on the literature study

- *The first specific objective of the literature study was to conceptualise pain and the treatment protocols thereof from available literature.*

This was done through an extensive literature review (refer to Chapter 2). Pain was classified, the social, economical and motivational implications of pain were investigated and the treatment and management of pain was discussed (refer to section 2.2).

Pain classifications have been based on duration, etiology or pathophysiology, intensity and symptoms which make the effective treatment of pain more complicated. Furthermore, the different types of pain can merge and many people suffer from combinations of acute and chronic pains, neuropathic and nociceptive pain. Therefore, the skills and ability of the practitioner or pharmacist to classify the pain determines the most appropriate outcome for each patient (refer to section 2.2.2).

According to Ables *et al.* (2006:341) "*pain is among the most common complaints in health care*". It accounts for considerable suffering and discomfort for patients, increased health care costs, a loss of productivity and is often associated with low self rated health. Pain is a major reason to visit a physician, thus the treatment of pain has a great economic impact on the health care system (refer to section 2.2.4).

Pain is most often managed with pharmaceutical products, although they are often used in combination with other therapies. According to Tintinalli *et al.* (2006) the primary agents for the control of pain are the opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (refer to section 2.3).

The literature study revealed that the efficacy of analgesics for mild to moderate pain is more or less equivalent. This should be kept in mind when prescribing combination analgesics for specific categories of pain, because there are price differences among combination analgesics which have the same efficacy.

- *The second specific objective of the literature study was to review combination analgesics and conceptualise the usage from the literature*

In section 2.4 the rationale behind combining analgesics, the basic pharmacology of combination analgesics and their ingredients, the advantages and disadvantages of combining analgesics and the toxic effects of these drugs were discussed. The usage of analgesics internationally and the abuse of analgesics was also included in the discussion (refer to sections 2.5 and 2.6).

The literature study revealed that the rationale behind combining drugs in pain management is based on two considerations. Firstly, combining drugs that act at different receptors and on different pain mechanisms may improve pain relief. Secondly, single drugs that provide acceptable pain relief may, at the same time, cause unacceptable side effects. Therefore, drug combinations may allow a decrease in the amount of the single components needed to achieve the same analgesic effect with a lower incidence of side effects (refer to section 2.4.1).

A combination analgesic is most effective when the individual agents act through different analgesic mechanisms and act synergistically. By activating multiple pain inhibitory pathways, combination analgesics can provide more effective pain relief for a broader spectrum of pain, and might also reduce adverse drug reactions.

The scheduling status of analgesics and combination analgesics in South Africa, the patient characteristics of prescription drug abusers, over-the-counter (OTC) analgesic abuse, opioid addiction and the dangers associated with analgesic abuse was discussed in section 2.6.

- *The third specific objective of the literature study was to review the South African health care system; with special reference to the private health care system.*

A concise overview regarding the public and private health care sectors in South Africa was discussed in section 3.2.1 and 3.2.2. Health care expenditure, equity in health, public-private partnerships, the drug pricing structure and the challenges which the South African health care system face were included in the discussion (refer to sections 3.2.3 to 3.2.8).

South Africa has a private and a public health care system with a grave discrepancy between the two, which reflects the country's first world/third world dichotomy. The public health care system is financed mainly by government subsidies and serves the mass of the population, while the private health care system is administered by health insurance programmes and only serves a small number of people who can pay for medical aid coverage/insurance.

The most important challenge facing the South African health system is to tackle the unproductive and unfair distribution of resources between the public and private health care sectors relative to the population served by each. Incompetence in the national health system threatens its sustainability since it leads to misdistribution of resources, and undermines policies and procedures intended to give effect to the distribution, allocation or utilisation of resources.

- *The fourth specific objective of the literature study was to conceptualise managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology from the literature; with special reference to the usage of combination analgesics.*

In a literature review of managed health care, drug utilisation review, pharmacoeconomics and pharmaco-epidemiology, it was established that these methods and techniques play an integral role in ensuring optimal health care (refer to sections 3.3 to 3.6).

Managed health care has been described as systems and techniques used to control the use of health care services. Managed care encompasses many diverse types of organisations, payment mechanisms, review mechanisms and collaborations. The primary objective of managed health care is the containment of health care costs and promoting the provision of quality health care services at affordable levels.

Drug utilisation review (DUR) provides a method for studying drug use through the review of medical and pharmaceutical records, with the goal of quantifying the medical and cost-effectiveness of drug therapy. Drug utilisation research is an essential part of pharmaco-

epidemiology as it describes the extent, nature and determinants of drug exposure.

Pharmacoeconomics has been formally defined by Bootman *et al.* (1996:4) as "*the description and analyses of the costs of drug therapy to healthcare systems and society.*" Pharmacoeconomics is a developing discipline that is committed to the study of how different approaches to patient care and treatment influence the resources consumed in healthcare (Truter, 1997:19). The ultimate objective of pharmacoeconomics is to assist the decision makers in achieving allocation efficiency in the healthcare system (Li, 2003:192).

Pharmaco-epidemiology is a study field, with concepts, methods and applications that have made great contributions to healthcare. Pharmaco-epidemiology applies epidemiological methods to studies of the clinical use of drugs in populations. Pharmaco-epidemiology may be drug-oriented, emphasising the safety and effectiveness of individual drugs or groups of drugs, or utilisation-oriented aiming to improve the quality of drug therapy through educational intervention (WHO, 2003:8).

6.2.2 Conclusions based on the empirical investigation

- *The first specific objective of the empirical investigation was to investigate the prevalence and cost relationship of combination analgesics in relation to all the medicine items on the database.*

This was described in Chapter 5. During the analysis of the general medicine prescribing patterns of the total database, it was evident that combination analgesics contribute considerably to the total cost and prevalence of all the medicine items available on the database.

Combination analgesics constituted for 8.87% (n=261 907) during 2001, 7.87% (n=317 997) during 2002, 7.20% (n=381 809) during 2004, 7.81% (n=281 590) during 2005 and 7.92% during 2006 (refer to section 5.2.1.3).

Combination analgesics represented 4.95% (n=R18 798 202.42) during 2001, 4.10% (n=R24 654 906.68) during 2002, 3.22% (n=R21 288 560.33) during 2004, 3.52% (n=R14 265 812.95) during 2005 and 3.15% (n=R 8 791 228.57) during 2006 of the total cost of all medicine items claimed through the database (refer to section 5.2.6.3).

- *The second objective of the empirical investigation was to investigate the prevalence and cost relationship of the*

combination analgesics in relation to analgesic medicine items on the database.

During the analysis of the prevalence and cost relationship of combination analgesics in relation with analgesics, it was evident that combination analgesics contribute considerably to the total cost and prevalence of all analgesics claimed through the database.

The number of combination analgesic medicine items represented 81.00% (n=261907) during 2001, 80.62% (n=317997) during 2002, 79.92% (n=381809) during 2004, 80.15% (n=281590) during 2005 and 79.43% (n=187 745) during 2006 of the total number of analgesic medicine items claimed through the total database (refer to section 5.2.1.3). This value reinforced Truter's finding of 81.2% in a South African study conducted in 1995 (Truter, 1996:1394).

Combination analgesic medicine items represented 89.60% (n=R18 798 202.42) during 2001, 87.98% (n=R24 654 906.68) during 2002, 84.65% (n=R21 288 560.33) during 2004, 84.82% (n=R14 265 812.95) during 2005 and 82.65% (n=R 8 791 228.57) during 2006 of the total cost of all analgesic medicine items claimed (refer to section 5.2.6.3).

- *The third specific objective of the empirical investigation was to compare the cost impact of the usage of generic combination analgesics and innovator products.*

In the analysis of combination analgesics according to their innovator/generic classifications it was found that the majority of combination analgesics prescribed during the study period 2001-2002 and 2004-2005 were innovator products. In 2006, generic combination analgesics had a higher prevalence than innovator products (refer to section 5.2.5.3).

The prevalence of innovator combination analgesics represented 70.37% (n=184 299) during 2001, 64.82% (n=206 124) during 2002, 63.29% (n=241 664) during 2004, 55.75% (n=156 995) during 2005 and 33.63% (n=63 145) for 2006 of all combination analgesic medicine items claimed. Generic combination analgesic medicine items represented 29.63% (n=77 608) during 2001, 35.18% (n=111 873) during 2002, 36.71% (n=140 145) during 2004, 44.25% (n=124 635) during 2005 and 66.37% (n=124 600) during 2006 of all combination analgesic medicine items claimed (refer to section 5.2.5.3).

The total cost of innovator combination analgesic medicine items represented 84.85% (n=R15 949 494.20) during 2001, 79.39% (n=R19 572 876.29) during 2002, 79.21% (n=R16 862 405.09)

during 2004, 70.88% (n=R 10 111 090.26) during 2005 and 45.82% (n=R 4 027 734.10) during 2006 of the total cost of all combination analgesic medicine items for the corresponding year. The cost percentage decrease corresponds with the decrease in the prevalence of innovator combination analgesics from 2001 to 2006. The total cost of generic combination analgesic medicine items represented 15.15% (n=R2 848 708.22) during 2001, 20.61% (n=R5 082 030.39) during 2002, 20.79% (n=R4 426 155.24) during 2004, 29.12% (n=R4 154 722.69) during 2005 and 54.18% (n=R 4 763 479.17) during 2006 of the total cost of all combination analgesic medicine items for the corresponding year (refer to section 5.3.1.3).

- *The fourth specific objective of the empirical investigation was to compare the cost-analysis of the different active ingredient combinations.*

In the analysis of combination analgesics according to their different active ingredient classifications it was found that the combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg represented the active ingredient combination with the highest prevalence for the entire study period, being 74483 (28.44%; N=261907) for 2001, 80151 (25.20%; N=317997) for 2002, 102416 (26.82%; N=381809) for 2004, 85792 (30.53%; N=281590) for 2005 and 62 100 (33.08%; n=187 745) for 2006. This combination also represented the active ingredient combination with the highest total cost for the entire study period, being R6 389 053.43 (33.99%; N=R 18 798 202.42) for 2001, R7 337 687.66 (29.76%; N=R24 654 906.68) for 2002, R6626117.34 (31.13%; N=R21 288 560.33) for 2004, R5 286 502.33 (37.06%; N=R14 265 812.95) for 2005 and R 2971412.87 (33.80%; N=R 8 91 228.57) for 2006. The combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg has a cost-prevalence index > 1 for the entire study period, indicating that it is relatively expensive (refer to section 5.3.2).

In the years 2001, 2002, 2005 and 2006 the combination of propoxyphene HCl 65mg, aspirin 375mg and caffeine 30mg represented the highest average cost of R202.37 ± 141.56, R252.90 ± R188.98, R158.79 ± 116.06 and R159.81 ± 103.43 respectively. The combination of aspirin 200mg, paracetamol 200mg, chlorphenoxamine HCL 2mg, codeine phosphate 15mg, caffeine 50mg and phenobarbitone 5mg represented the highest average cost of R283.45 ± 345.49 for 2004 (refer to section 5.3.2).

- *The fifth specific objective of the empirical investigation was to analyse the usage and prescription patterns of different*

combination analgesic brand names as well as the costs associated with these drugs according to the database.

The forty-two combination analgesics were discussed in section 5.3.3 according to the different brand names.

- *The sixth specific objective of the empirical investigation was to analyse the average number of combination analgesic prescriptions per patient per year.*

During the analysis of the average number of combination analgesic prescriptions per patient per year, it was established that number of prescriptions (containing any medicine item(s)) per patient per year was much higher.

The number of prescriptions (containing any medicine item(s)) per patient per year decreased from 4.37±4.45 in 2001 to 3.94±4.27 in 2004 after which it increased to 4.26±4.87 in 2005. From 2005 to 2006 the average number of prescriptions per patient decreased from 4.26±4.87 to 3.76±4.56.

The number of combination analgesic prescriptions per patient per year decreased from 1.91±1.73 in 2001 to 1.63±1.34 in 2004 after which it increased to 1.79±1.65 in 2005. From 2005 to 2006, there was a slight decrease to 1.77±1.65 combination analgesic prescriptions per patient per year. The strict control of schedule 5 and specified schedule 5 medicine items implemented in 2003 might have influenced the decrease in combination analgesic prescriptions per patient per year between 2002 and 2004.

- *The seventh specific objective of the empirical investigation was to identify combination therapy of analgesics and determine the costs associated with these combinations.*

A total of 452965, 332059 and 223746 of the prescriptions issued for the respective years 2004, 2005 and 2006 were for analgesic mono-therapy which amounted to R23 593 107.6, R15 712 953.41 and R9 869 250.05 respectively (refer to section 5.4.1). Analgesic mono-therapy represented more than 97% of the total number of analgesic containing prescriptions from 2004 to 2006.

A possible explanation for the high percentage of analgesics prescribed as mono-therapy, might be the fact that 76.73% (n=347566), 80.99% (n=268927) and 80.19% (n=179420) of al analgesic mono-therapies for the respective years 2004, 2005 and 2006 was for combination analgesics, which already contain more than one analgesic active ingredient.

Seven out of the top-ten most frequently prescribed analgesic mono-therapies prescribed in 2004 were combination analgesics. In 2005 and 2006 eight out of the top-ten most frequently prescribed analgesic mono-therapies prescribed were combination analgesics.

Analgesic double and triple combination therapy had low prevalence's, representing less than 3% of the total number of prescriptions containing at least one analgesic medicine item from 2004 to 2006 (refer to section 5.4.1).

- *The eighth specific objective of the empirical investigation was to analyse the prevalence of combination analgesics available without prescription.*

In the analysis of combination analgesics according to their scheduling status it was found that the majority of combination analgesics claimed during the study period 2001-2002 and 2004-2006 were available over-the-counter (S0, S1 or S2).

For the respective years 2001, 2002, 2004, 2005 and 2006, 67.00%, 84.31%, 70.80%, 73.88% and 79.96% were available over-the-counter.

The high prescribing rate and use of combination analgesics is a cause for concern, due to the dependence-producing potential of some of the ingredients.

- *The ninth specific objective of the empirical investigation was to identify possible other outstanding aspects that may require further investigation.*

During the completion of this study, recommendations were formulated, with special focus on the optimisation of combination analgesic utilisation. A discussion of these recommendations will follow in section 6.4.

6.3 Limitations of the research study

Based on the results and discussion of this study, certain limitations were identified, which could restrict or limit the scope of this study. These limitations should be taken into account when evaluating the results and conclusions because they can possibly have an effect on the results and conclusions obtained through this study.

The following limitations were detected:

- The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for the whole 2003, therefore the usage and costs of drugs associated with this period cannot be compared with the other periods.

- No clinical data or demographic information, such as age, gender and race was available on the database, therefore the relevance of some of the utilisation patterns could not be determined.
- The data concerning the usage and cost of medicine items which were obtained from the medicine claims database was considered to be correct and accurate (refer to section 4.8).
- Data for the analysis were obtained from one medicine claims database, thus, limiting external validity, implying that results can only be generalised to the specific database used, as well as to the specific study population.
- The database lack information on the prevalence of adverse effects, follow-up treatment caused by adverse effects of the combination analgesics and the efficacy of combination analgesics, and thus any evaluation thereof could not be done. The only conclusion therefore could be made from the literature study and the prevalence and frequency of analgesics prescribed.

6.4 Recommendations

The following recommendations can be made after the completion of this study for further research on aspects that were not investigated in this study due to the limited scope, nature and extent of this study:

- The implication of generic substitution with regard to cost and prescribing patterns need further investigation.
- The decreasing cost of combination analgesics might encourage abuse, this needs further investigation.
- The need for public and professional education regarding the correct and safe usage of combination analgesics is strongly recommended.
- The inclusion of the prevalence of adverse reactions and the measurement of pain efficacy should be taken into consideration for future studies.
- Further studies can be undertaken to investigate the outcomes of pain management with regard to the dosage routes and severity of drug interactions, as well as to determine the accuracy of pain diagnosis of physicians.
- Studies can be undertaken to determine the appropriate and necessary usage of combination analgesics in the private health care sector.

6.5 Chapter summary

In this final chapter, the conclusions of the specific objectives of the study were drawn and discussed. Recommendations that were derived regarding certain aspects of the clinical and economical management of pain, as well as the limitations that were encountered during the course of the study have been discussed

Hereby the specific research objectives were reached.

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APPENDIX

Appendix A: Utilisation of one analgesic agent in mono-therapy for the years 2004, 2005 and 2006.

Appendix B: Utilisation of two analgesic agents in double-therapy for the years 2004, 2005 and 2006.

Appendix C: Utilisation of three analgesic agents in triple-therapy for the years 2004, 2005 and 2006.

Appendix D: Utilisation of four analgesic agents in combination-therapy for the years 2004, 2005 and 2006.

Appendix E: Utilisation of five analgesic agents in combination-therapy for the years 2005 and 2006.

Appendix F: Abstract as presented during the Young Scientist Competition at the Academy of Pharmaceutical Sciences Conference – 6 September 2007.

Table A1 Utilisation of one analgesic agent in mono-therapy for the year 2004.

Agents in mono-therapy	Number of Rx	Average cost (R)	Total cost (R)
Aspirin/Caffeine	10	21.75±13.13	217.53
Aspirin 500mg/Codeine 8mg	719	35.86±20.99	25780.68
Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	8	303.63±363.63	2429.05
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	184	42.85±8.61	7883.92
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	162	83.63±63.74	13548.26
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1089	77.48±57.79	843080.52
Aspirin	11612	11.32±7.85	131480.57
Buprenorphine	146	287.3±229.39	41945.32
Codeine	332	194.49±196.38	64571.78
Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg	9	35.6±16.13	320.39
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	9457	159.26±115.79	1506088.49
Dihydrocodeine tartrate	118	170.58±124.20	20128.48
Dipanone HCl/Cyclizine	46	207.79±143.34	9558.52
Fentanyl	207	848.44±553.79	175626.21
Ibuprofen 200mg/Paracetamol 250mg	29625	54.69±21.09	1620189.96
Ibuprofen 200mg/Paracetamol 350mg	78	29.59±10.41	2308.42
Ibuprofen 400mg/ Paracetamol 325mg	5733	40.47±25.07	346688.23
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	99540	64.45±27.58	6415324.62
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	48692	48.67±20.16	2370076.39

Table A1 Utilisation of one analgesic agent in mono-therapy for the year 2004.

Agents in mono-therapy	Number of Rx	Average cost (R)	Total cost (R)
Ibuprofen	2966	30.65±21.39	90918.45
Ibuprofen 200mg/Codeine phosphate 10mg	9	41.09±34.49	369.77
Ketorolac tromethane	242	137.03±100.28	33161.79
Mefenamic acid	32025	28.59±27.27	915599.78
Morphine	248	561.21±622.24	139180.82
Morphine sulphane	39	216.97±286.67	8461.95
Morphine/ Cyclizine	9	60.43±69.10	543.87
Morphine/ Papaveratum/Codeine	11	1264.53±916.18	13909.88
Orphenadrine 35mg/Paracetamol 450mg	9401	37.72±16.28	354609.34
Paracetamol/Aspirin/Caffeine	2	1.36±0.00	2.72
Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	141	29.09±16.99	4101.2
Paracetamol 120mg/Codeine phosphate 5mg	23	17.01±6.18	391.15
Paracetamol 320mg/Codeine phosphate 8mg	457	28.24±40.55	12904.5
Paracetamol 500mg/Codeine phosphate 10mg	2979	13.4±9.34	39916.97
Paracetamol 500mg/Codeine phosphate 20mg	679	47.24±25.86	32072.69
Paracetamol 500mg/Codeine phosphate 8mg	3669	25.74±17.23	94432.4
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	330	39.75±28.87	13117.42
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	7245	77.63±63.39	562432
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	5678	23.83±32.23	1352238.21

Table A1 Utilisation of one analgesic agent in mono-therapy for the year 2004.

Agents in mono-therapy	Number of Rx	Average cost (R)	Total cost (R)
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	5004	43.88±32.67	219563.75
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2243	65.89±49.05	147799.92
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	2613	36.25±31.13	94729.64
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	20093	21.87±15.08	439336.77
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	17460	129.52±86.37	2261342.51
Paracetamol 120mg/ Doxylamine succinate 5mg	1	30.21±0.00	30.21
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	26205	38.28±34.25	1003224.75
Paracetamol 500mg/ Mephenesin 150mg	2631	32.99±17.68	86810.87
Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	567	54.88±33.36	31118.08
Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	515	19.97±11.59	10283.84
Paracetamol	32526	14.61±15.03	475146.62
Paracetamol/Codeine phosphate/Caffeine	427	68.99±30.47	29458.63
Pentazocine	22	57.13±42.44	1256.86
Pethidine	187	39.48±58.02	7382.23
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	907	54.17±114.56	139833.72
Propoxyphene HCl 50mg/ Paracetamol 325mg/	497	96.21±67.08	47815.54
Propoxyphene HCl 65mg/ Paracetamol 250mg/	3547	154.97±122.08	549680.08
Propoxyphene	348	174.33±156.58	60666.09
Tilidine	310	368.11±558.95	114113.42

Table A1 Utilisation of one analgesic agent in mono-therapy for the year 2004.

Agents in mono-therapy	Number of Rx	Average cost (R)	Total cost (R)
Paracetamol 325mg/Tramadol HCL 37.5mg	6411	70.63±44.12	452807.53
Tramadol	5461	167.33±164.68	913794.29

Table A2 Utilisation of one analgesic agent in mono-therapy for the year 2005.

Agent in monotherapy	Number of Rx	Average cost (R)	Total cost (R)
Aspirin/Caffeine	1	9.04±0.00	9.04
Aspirin 500mg/Codeine 8mg	444	31.24±18.77	13870.5
Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	1	111.8±0.00	111.8
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	60	33.41±9.96	2004.65
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	107	66.35±87.26	7099.83
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1091	64.58±40.56	70462.01
Aspirin	4169	10.55±8.13	43990.93
Buprenorphine	45	270.6±239.51	12177.28
Codeine	136	117.13±108.87	15929.56
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	5827	153.42±106.78	894007.35
Dihydrocodeine tartrate	76	167.19±97.14	12706.34
Dipanone HCl/Cyclizine	28	219.62±85.33	6149.46
Fentanyl	156	894.65±982.01	139565.51
Ibuprofen 200mg/Paracetamol 250mg	23601	44.05±23.02	1039739.14
Ibuprofen 200mg/Paracetamol 350mg	1869	35.32±14.54	66030.74
Ibuprofen 400mg/ Paracetamol 325mg	4133	57.26±21.35	236679.42
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	83609	61.23±26.95	5119199.14
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	42721	48.38±19.05	2066727.02
Ibuprofen	2018	23.04±14.17	46503.2

Table A2 Utilisation of one analgesic agent in mono-therapy for the year 2005.

Agent in monotherapy	Number of Rx	Average cost (R)	Total cost (R)
Ibuprofen 200mg/Codeine phosphate 10mg	466	32.17±11.42	14993.17
Ketorolac tromethane	186	102.05±76.82	18879.37
Mefenamic acid	25238	23.33±19.48	588850.68
Morphine	81	474.95±553.79	38471.05
Morphine sulphane	38	209.18±245.88	7948.97
Morphine/ Cyclizine	7	56.77±46.12	397.39
Morphine/ Papaveratum/Codeine	36	457±561.62	16451.91
Orphenadrine 35mg/Paracetamol 450mg	8690	34.09±14.29	296253.64
Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	27	25.47±14.26	687.81
Paracetamol 120mg/Codeine phosphate 5mg	2	19.29±11.70	38.59
Paracetamol 320mg/Codeine phosphate 8mg	236	19.74±37.52	4658.84
Paracetamol 500mg/Codeine phosphate 10mg	1605	10.63±12.82	17059.22
Paracetamol 500mg/Codeine phosphate 20mg	315	49.79±29.12	15683.14
Paracetamol 500mg/Codeine phosphate 8mg	2079	24.11±16.49	50114.81
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	168	27±15.02	4536.17
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	6007	62.28±42.11	380129.08
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	34259	19.41±23.46	664849.31
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1172	34.03±28.39	29879.62
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	782	88.24±101.33	69005.32

Table A2 Utilisation of one analgesic agent in mono-therapy for the year 2005.

Agent in monotherapy	Number of Rx	Average cost (R)	Total cost (R)
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	321	9.49±4.16	3047.35
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	12691	15.53±10.42	197173.26
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	10166	116.18±69.87	1181094.62
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	17166	27.56±24.13	473107.54
Paracetamol 500mg/ Mephenesin 150mg	1175	24.53±13.65	28818.17
Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	92	55.82±44.72	5135.16
Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	440	14.93±6.29	5671.17
Paracetamol	25814	11.9±13.99	307310.84
Paracetamol/Codeine phosphate/Caffeine	127	58.72±21.68	7457.68
Pentazocine	4	57.72±58.35	230.86
Pethidine	145	18.46±23.71	2677.2
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	423	159.58±117.13	67502.68
Propoxyphene HCl 50mg/ Paracetamol 325mg/	324	70.65±29.65	22890.67
Propoxyphene HCl 65mg/ Paracetamol 250mg/	1278	140.2±105.62	179172.66
Propoxyphene	95	258.28±234.16	24536.63
Tilidine	120	211.25±240.29	25350.39
Paracetamol 325mg/Tramadol HCL 37.5mg	5452	67.06±55.08	365589.97
Tramadol	4740	169.69±162.69	804335.55

Table A3 Utilisation of one analgesic agent in mono-therapy for the year 2006.

Agents in combination	Number of Rx	Average cost (R)	Total cost (R)
Aspirin 500mg/Codeine 8mg	149	32.56±12.72	4851.12
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	16	26.14±12.22	418.28
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	6	69.99±64.15	419.94
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	322	85.17±86.37	27425.99
Aspirin	905	15.47±11.11	13995.98
Buprenorphine	23	298.01±177.10	6845.23
Codeine	71	203.8±112.32	14469.73
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	3390	173.49±107.69	588120.29
Dihydrocodeine tartrate	12	97.79±60.59	1173.49
Dipanone HCl/Cyclizine	2	228.54±82.17	457.07
Fentanyl	106	1137.38±1134.22	120562.46
Ibuprofen 200mg/Paracetamol 250mg	18965	23.81±25.85	451467.51
Ibuprofen 200mg/Paracetamol 350mg	991	35.84±14.06	35514.11
Ibuprofen 400mg/ Paracetamol 325mg	2661	62.85±22.34	167249.91
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	60556	47.73±17.09	2890093.08
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	31067	54.72±31.42	1699943.77
Ibuprofen	848	26.55±14.23	22516.13
Ibuprofen 200mg/Codeine phosphate 10mg	323	38.8±12.01	12531.27
Ketorolac tromethane	75	69.93±99.94	5245.19

Table A3 Utilisation of one analgesic agent in mono-therapy for the year 2006.

Agents in combination	Number of Rx	Average cost (R)	Total cost (R)
Mefenamic acid	19096	21.99±17.80	420020.31
Morphine	32	478.41±306.44	15309.02
Morphine sulphate	11	19.47±24.57	214.18
Morphine/ Papaveratum/Codeine	8	1331.3±813.59	10650.39
Orphenadrine 35mg/Paracetamol 450mg	6965	34.12±13.05	237572.24
Paracetamol 320mg/Codeine phosphate 8mg	56	13.71±7.62	768.03
Paracetamol 500mg/Codeine phosphate 10mg	1097	11.99±3.99	13153.54
Paracetamol 500mg/Codeine phosphate 20mg	149	55.58±26.39	8281.99
Paracetamol 500mg/Codeine phosphate 8mg	756	24.25±15.64	18334.81
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	94	35.69±23.78	3355.47
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2070	69.99±51.06	144876.12
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	17023	24.06±28.80	409631
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	523	42.38±30.80	22165.28
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	752	99.49±59.66	74817.85
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	59	10.05±4.95	593.21
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6915	15.17±8.06	104867.75
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3495	132.96±83.96	464702.06
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	13906	31.36±25.82	436096.49
Paracetamol 500mg/ Mephenesin 150mg	462	27.7±20.48	12796.16

Table A3 Utilisation of one analgesic agent in mono-therapy for the year 2006.

Agents in combination	Number of Rx	Average cost (R)	Total cost (R)
Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	11	23.06±12.65	253.65
Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	116	17.36±8.36	2014.24
Paracetamol	19295	13.06±31.69	251975.01
Paracetamol/Codeine phosphate/Caffeine	32	53.08±19.69	1698.52
Pentazocine	1	16.43±0.00	16.43
Pethidine	160	14.23±25.77	2276.85
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	314	160.81±102.17	50495.09
Propoxyphene HCl 50mg/ Paracetamol 325mg/	119	81.87±52.46	9742.47
Propoxyphene HCl 65mg/ Paracetamol 250mg/	285	146.29±103.91	41691.98
Propoxyphene	59	250.01±173.72	14750.36
Tilidine	54	195.36±186.47	10549.27
Paracetamol 325mg/Tramadol HCL 37.5mg	5775	77.02±68.96	444765.26
Tramadol	3568	161.86±167.39	577514.47

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin/Caffeine	Aspirin 500mg/Codeine 8mg	1	60.07±0.00	60.07
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	63.60±0.00	63.60
	Paracetamol 500mg/ Mephenesin 150mg	1	60.15±0.00	60.15
Aspirin 500mg/Codeine 8mg	Aspirin	1	108.91±0.00	108.91
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	1	369.20±0.00	369.20
	Ibuprofen 200mg/Paracetamol 250mg	7	79.24±31.66	554.66
	Ibuprofen 400mg/Paracetamol 325mg	1	124.65±0.00	124.65
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	14	104.92±39.05	1468.94
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	3	77.12±25.26	23.36
	Ibuprofen	1	100.15±0.00	100.15
	Mefenamic acid	1	181.61±0.00	181.61
	Orphenadrine 35mg/Paracetamol 450mg	4	143.52±30.46	574.08
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	7	66.45±17.31	465.15
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	89.43±28.89	178.85
	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	82	104.11±71.06	8537.09
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	267.38±150.96	534.75
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	10	109.28±68.83	1092.81
	Paracetamol	22	48.50±20.86	1067.78
	Paracetamol/Codeine phosphate/Caffeine	1	54.53±0.00	54.53
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	80.46±0.00	160.92
	Tramadol	1	148.50±0.000	148.50
Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	224.57±0.00	224.57

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	6	103.48±10.28	620.85
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	1	94.60±0.00	94.60
	Ibuprofen	1	46.28±0.00	46.28
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	59.34±0.00	118.68
	Paracetamol	1	43.97±0.00	43.97
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Ibuprofen 200mg/Paracetamol 250mg	2	240.91±39.55	481.81
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	106.98±0.00	106.98
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	280.52±0.00	280.52
	Tramadol	1	601.69±0.00	601.69
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Fentanyl	1	569.74±0.00	569.74
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	11	143.65±59.82	1580.17
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	12	100.48±23.58	1205.77
	Orphenadrine 35mg/Paracetamol 450mg	4	77.72±11.72	310.89
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	4	150.04±32.98	600.16
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	3	156.55±100.82	469.64
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	4	70.88±11.40	283.50
	Tramadol	1	415.59±0.00	415.59
Aspirin	Aspirin	2	66.61±76.68	133.22
	Buprenorphine	1	67.73±0.00	67.73
	Codeine	2	37.20±2.77	74.39
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	6	239.19±282.96	1435.16
	Ibuprofen 200mg/Paracetamol 250mg	30	97.2±40.493	2916.07
	Ibuprofen 400mg/ Paracetamol 325mg	5	81.12±5.76	405.61
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	41	85.24±31.09	3494.92

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin (continued)	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	26	60.27±16.27	1566.89
	Ibuprofen	7	74.66±53.49	522.61
	Mefenamic acid	9	61.82±30.71	556.40
	Orphenadrine 35mg/Paracetamol 450mg	8	62.76±13.79	502.04
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	7	62.28±12.16	435.98
	Paracetamol 320mg/Codeine phosphate 8mg	1	20.05±0.00	20.05
	Paracetamol 500mg/Codeine phosphate 10mg	5	24.35±8.36	121.75
	Paracetamol 500mg/Codeine phosphate 20mg	5	144.42±15.12	572.12
	Paracetamol 500mg/Codeine phosphate 8mg	15	47.74±23.36	716.12
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	5	191.78±114.47	958.91
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	53	32.3±31.68	1711.81
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	8	105.2±64.29	841.63
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	6	69.64±34.81	417.86
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6	64.72±26.58	388.33
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	12	148.14±94.25	1777.68
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	75	75.02±45.55	5626.61
	Paracetamol 500mg/ Mephenesin 150mg	6	65.79±32.34	394.74
	Paracetamol	83	36.89±24.13	3061.65
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	9	165.72±69.38	1491.47
	Paracetamol 325mg/Tramadol HCL 37.5mg	6	94.05±33.95	564.31
	Tramadol	9	171.17±188.94	1540.51
Buprenorphine	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	3	383.95±187.43	1151.84
	Fentanyl	6	1313.13±316.33	7878.80
	Ibuprofen 200mg/Paracetamol 250mg	1	159.43±0.00	159.43
	Ibuprofen 400mg/ Paracetamol 325mg	1	146.15±0.00	146.15
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	3	111.99±30.29	335.98
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	1	385.23±0.00	385.23

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Buprenorphine (continued)	Morphine/Papaveratum/Codeine	1	1063.61±0.00	1063.61
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	268.77±47.39	1075.06
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	115.66±89.00	231.32
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	747.73±0.00	747.73
	Tramadol	3	556.46±171.86	1669.38
Codeine	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	1	127.33±0.00	127.33
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	6	98.29±33.66	598.76
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	3	139.98±30.79	419.68
	Mefenamic acid	3	112.91±19.66	338.73
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	56.16±7.39	112.31
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	85.22±0.00	85.22
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	215.22±0.00	215.22
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	205.21±133.47	410.41
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	190.59±193.95	381.17
	Paracetamol	5	62.06±23.78	310.29
	Tramadol	1	140.99±0.00	140.99
Dextropropoxyphene HCl 65mg/ Paracetamol 300mg/ Caffeine 30mg	Ibuprofen 200mg/Paracetamol 250mg	6	91.77±7.23	550.61
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	4	79.20±10	316.78
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	50.99±10.61	101.98
	Paracetamol/Codeine phosphate/Caffeine	3	72.62±11.22	217.87
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Dihydrocodeine tartrate	3	220.91±26.50	662.73
	Dipipanone HCl/Cyclizine	1	416.16±0.00	416.16
	Fentanyl	11	993.74±444.11	10931.09

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg (continued)	Ibuprofen 200mg/Paracetamol 250mg	12	283.92±152.81	3407.09
	Ibuprofen 400mg/ Paracetamol 325mg	17	209.82±123.55	3567.02
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	149	225.23±155.93	33559.18
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	21	204.21±100.56	4288.31
	Ibuprofen	2	130.27±13.15	260.54
	Ketorolac Thomethane	5	483.24±271.88	2416.19
	Mefenamic acid	20	187.71±106.52	3754.17
	Morphine	7	1045.78±500.64	7320.43
	Orphenadrine 35mg/Paracetamol 450mg	26	271.08±302.80	7048.16
	Paracetamol 320mg/Codeine phosphate 8mg	2	148.03±0.00	296.06
	Paracetamol 500mg/Codeine phosphate 10mg	1	101.41±0.00	101.41
	Paracetamol 500mg/Codeine phosphate 20mg	2	108.48±21.83	216.95
	Paracetamol 500mg/Codeine phosphate 8mg	3	178.56±70.30	535.69
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	7	486.48±373.75	3405.35
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	69	209.00±170.80	14421.14
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	214.18±0.00	214.18
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	3	89.82±3.57	269.45
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	4	122.38±35.06	489.51
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	5	212.01±141.96	1060.05
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	35	282.12±196.50	9874.32
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	7	193.22±106.25	1352.57
	Paracetamol 500mg/ Mephenesin 150mg	4	116.53±62.69	466.10
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	204.49±0.00	204.49
	Paracetamol	13	178.072±138.92	2314.92
	Paracetamol/Codeine phosphate/Caffeine	1	273.51±0.00	273.51

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
	Pethidine	5	146.66±109.76	733.28
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	499.48±202.59	998.95
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg (continued)	Propoxyphene HCl 65mg/ Paracetamol 250mg/	5	496.55±439.32	2482.76
	Propoxyphene	1	117.62±0.00	117.62
	Tilidine	3	526.43±419.47	1579.30
	Paracetamol 325mg/Tramadol HCL 37.5mg	25	156.03±63.86	3900.70
	Tramadol	87	335.75±309.00	29210.65
Dihydrocodeine tartrate	Ibuprofen 200mg/Paracetamol 250mg	2	74.62±0.00	74.24
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	4	119±69.29	475.99
	Morphine sulphate	1	49.43±0.00	49.43
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	5	169.39±67.26	846.94
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	929.13±2.60	1858.26
	Paracetamol	3	56.54±7.86	169.63
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	226.09±0.00	226.09
	Tramadol	1	717.54±0.00	717.54
Dipanone HCl/Cyclizine	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	155.66±0.00	155.66
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	148.76±0.00	148.76
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	96.96±0.00	96.96
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	212.81±150.20	425.63
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	135.91±0.00	135.91
Fentanyl	Fentanyl	8	2742.88±1581.90	21943.00
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	6	711.33±389.45	4267.95
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	4	1041.54±98.77	4166.15
	Morphine	3	1939.22±259.82	5817.66
	Morphine sulphate	1	136.68±0.00	136.68
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	6	241.58	3776.32

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Fentanyl (continued)	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	615.57±333.72	2462.27
	Paracetamol	2	575.88±0.00	1151.76
	Pethidine	1	580.22±0.00	580.22
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	921.48±304.25	3685.90
	Tramadol	1	724.99±0.00	724.99
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg	3	165.06±89.06	495.18
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	41	125.51±42.32	5145.83
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	10	110.03±27.79	1100.34
	Ibuprofen	8	127.11±54.78	1016.85
	Mefenamic acid	173	99.52±28.83	17216.73
	Orphenadrine 35mg/Paracetamol 450mg	101	89.36±30.83	9025.36
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	102.81±0.00	102.81
	Paracetamol 320mg/Codeine phosphate 8mg	1	59.17±0.00	59.17
	Paracetamol 500mg/Codeine phosphate 10mg	8	51.30±4.55	410.38
	Paracetamol 500mg/Codeine phosphate 20mg	1	125.10±0.00	125.10
	Paracetamol 500mg/Codeine phosphate 8mg	3	79.20±17.20	237.61
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	7	110.74±52.42	775.19
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	50	99.03±57.16	4951.55
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	17	109.95±41.81	1869.13
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	76.22±0.00	76.22
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	55.06±0.00	55.06
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	59	75.05±26.21	4427.76
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	14	200.29±159.93	2804.02
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	121	98.66±46.06	11937.78

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg (continued)	Paracetamol 500mg/ Mephenesin 150mg	45	92.17±50.24	4147.58
	Paracetamol	164	80.90±30.18	13266.88
	Paracetamol/Codeine phosphate/Caffeine	3	135.02±37.24	405.06
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	181.32±0.00	181.32
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	11	140.24±36.56	1542.66
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	3	137.41±25.55	412.24
	Propoxyphene	1	197.99±0.00	197.99
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	102.85±32.12	411.41
	Tramadol	39	382.91±290.43	14933.33
Ibuprofen 200mg/Paracetamol 350mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	43.49±0.00	86.98
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	38.75±0.00	38.75
	Paracetamol 500mg/ Mephenesin 150mg	2	33.85±9.84	67.69
	Paracetamol	1	48.36±0.00	48.36
Ibuprofen 400mg/ Paracetamol 325mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	3	118.27±31.91	354.80
	Mefenamic acid	5	70.27±31.91	351.33
	Orphenadrine 35mg/Paracetamol 450mg	38	100.97±47.65	3836.74
	Paracetamol 500mg/Codeine phosphate 10mg	1	101.69±0.00	101.69
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	11	243.19±118.35	2675.14
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	21	90.20±86.95	1384.07
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	59.57±4.45	119.13
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	241.33±0.00	482.66
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	80.97±0.00	80.97
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	15	234.78±186.78	3521.69
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	8	90.71±47.15	725.64
	Paracetamol 500mg/ Mephenesin 150mg	2	105.03±32.80	210.06

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 400mg/ Paracetamol 325mg (continued)	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	73.48±0.00	73.48
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	81.46±0.00	81.46
	Paracetamol	8	201.50±110.56	1612.01
	Pethidine	1	100.63±0.00	100.63
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	152.30±0.00	304.60
	Paracetamol 325mg/Tramadol HCL 37.5mg	8	112.14±13.97	897.10
	Tramadol	20	246.75±256.43	4935.08
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	20	150.86±70.85	3017.22
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	28	128.40±128.41	3595.09
	Ibuprofen	25	96.37±40.07	2409.27
	Ketorolac Thomethane	8	171.57±68.69	1372.57
	Mefenamic acid	232	98.82±38.61	22925.10
	Morphine	2	504.011±223.64	1008.03
	Orphenadrine 35mg/Paracetamol 450mg	243	99.54±36.61	24188.22
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	3	66.36±42.90	199.08
	Paracetamol 320mg/Codeine phosphate 8mg	5	55.84±14.93	279.18
	Paracetamol 500mg/Codeine phosphate 10mg	9	69.12±21.37	622.07
	Paracetamol 500mg/Codeine phosphate 20mg	4	90.65±2.75	362.61
	Paracetamol 500mg/Codeine phosphate 8mg	10	86.62±36.65	866.21
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	57	125.90±77.28	7176.47
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	464	102.94±61.63	47765.05
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	32	113.03±59.96	3616.95
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	21	153.63±95.80	3226.19
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	7	106.35±49.73	744.48
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	81	83.09±33.12	6729.90

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	291	199.07±98.43	75930.40
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	258	102.06±65.65	26331.44
	Paracetamol 500mg/ Mephenesin 150mg	39	97.80±30.02	3814.28
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	5	107.56±16.50	537.79
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	59.57±0.00	59.57
	Paracetamol	203	84.82±38.41	17218.22
	Paracetamol/Codeine phosphate/Caffeine	2	96.18±3.94	192.36
	Pentazocine	1	112.44±0.00	112.44
	Pethidine	2	71.98±23.44	143.95
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	4	283.79±161.14	1135.15
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	2	166.58±164.47	333.15
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	30	216.54±151.47	6496.10
	Propoxyphene	13	107.25±24.95	1393.92
	Tilidine	14	179.73±103.31	2516.25
	Paracetamol 325mg/Tramadol HCL 37.5mg	63	126.15±39.40	7947.65
	Tramadol	320	290.08±221.62	92824.14
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Ibuprofen	4	78.65±23.81	314.61
	Ketorolac Thomethane	5	151.56±51.91	757.81
	Mefenamic acid	44	79.21±34.96	3485.18
	Orphenadrine 35mg/Paracetamol 450mg	234	76.29±27.03	17851.75
	Paracetamol 320mg/Codeine phosphate 8mg	2	55.67±31.64	11.33
	Paracetamol 500mg/Codeine phosphate 10mg	9	96.13±38.03	865.18
	Paracetamol 500mg/Codeine phosphate 8mg	23	79.53±35.84	1829.26
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	3	75.80±0.00	227.40
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	18	154.20±110.94	2775.56
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	261	68.60±36.73	17904.71

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg (continued)	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	14	67.87±21.52	950.13
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	11	108.13±30.17	1189.41
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	9	44.59±9.49	401.33
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	9	65.17±33.34	586.52
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	94	147.82±73.60	13894.69
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	112	76.00±31.94	8511.55
	Paracetamol 500mg/ Mephenesin 150mg	22	74.82±23.02	1646.01
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	67.58±0.00	67.58
	Paracetamol	58	75.28±91.79	4366.25
	Paracetamol/Codeine phosphate/Caffeine	3	105.34±8.17	316.02
	Pethidine	1	103.18±0.00	103.18
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	127.13±0.00	127.13
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	4	125.19±32.20	500.75
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	13	128.09±48.15	1665.18
	Propoxyphene	3	137.19±22.80	411.57
	Tilidine	3	150.07±85.97	450.20
	Paracetamol 325mg/Tramadol HCL 37.5mg	33	146.45±107.13	4832.67
	Tramadol	194	176.73±144.74	34285.74
Ibuprofen	Mefenamic acid	29	70.34±30.19	2039.81
	Orphenadrine 35mg/Paracetamol 450mg	46	57.84±23.25	2646.73
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	41.43±0.00	41.43
	Paracetamol 320mg/Codeine phosphate 8mg	4	33.49±20.22	133.98
	Paracetamol 500mg/Codeine phosphate 10mg	3	56.24±26.20	168.71
	Paracetamol 500mg/Codeine phosphate 8mg	7	36.28±17.51	253.93
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	112.95±0.00	112.95

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	87	27.31±27.68	2375.95
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	13	33.73±15.22	438.44
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	62.84±0.00	62.84
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	141	57.42±34.96	8096.19
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	9	106.88±30.83	961.90
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	63	62.69±46.12	3949.85
	Paracetamol 500mg/ Mephenesin 150mg	9	76.57±44.27	689.10
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	24.06±0.00	24.06
	Paracetamol	111	46.72±29.88	5186.18
	Paracetamol/Codeine phosphate/Caffeine	1	172.88±0.00	172.88
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	70.45±21.98	281.78
	Tramadol	4	107.67±101.53	430.67
Ibuprofen 200mg/Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	47.34±0.00	47.34
Ketorolac tromethane	Ketorolac tromethane	1	224.5±0.00	224.35
	Orphenadrine 35mg/Paracetamol 450mg	1	84.5±0.00	84.50
	Paracetamol 500mg/Codeine phosphate 8mg	1	93.38±0.00	93.38
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	5	220.75±121.13	1103.74
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	151.86±0.00	151.86
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	20	253.91±69.17	4078.15
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	665.99±20.43	1331.99
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	2	27.96±0.00	55.92

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Ketorolac tromethane (continued)	Paracetamol	1	142.46±0.00	142.46
	Propoxyphene	1	382.13±0.00	382.13
	Tilidine	2	393.15±43.04	786.29
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	245.97±44.99	491.94
	Tramadol	14	144.5±174.03	2023.00
Mefenamic acid	Mefenamic acid	158	82.15±67.37	12979.67
	Orphenadrine 35mg/Paracetamol 450mg	41	96.93±58.47	3974.19
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	61.42±0.00	61.42
	Paracetamol 320mg/Codeine phosphate 8mg	2	32.73±2.81	65.45
	Paracetamol 500mg/Codeine phosphate 10mg	16	36.91±16.34	590.62
	Paracetamol 500mg/Codeine phosphate 20mg	11	96.86±48.90	1065.41
	Paracetamol 500mg/Codeine phosphate 8mg	20	40.43±15.64	808.62
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	15	90.83±42.32	1362.40
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	223	55.76±55.06	12433.87
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	26	60.26±38.67	1566.89
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	9	61.44±35.93	552.98
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	18	33.15±24.94	596.62
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	673	52.45±32.39	35302.13
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	46	107.35±51.53	4938.14
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	96	63.38±53.23	6084.51
	Paracetamol 500mg/ Mephenesin 150mg	12	46.29±20.40	555.52
	Paracetamol	969	57.32±34.97	55547.86
	Paracetamol/Codeine phosphate/Caffeine	1	220.25±0.00	220.25
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	114.13±0.00	114.13

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Mefenamic acid (continued)	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	151.57±0.00	151.57
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	8	92.13±51.64	737.00
	Tilidine	3	124.83±50.65	374.49
	Paracetamol 325mg/Tramadol HCL 37.5mg	10	80.19±33.40	801.48
	Tramadol	13	116.21±89.43	1510.78
Morphine	Morphine	14	1233.21±388.49	17264.94
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	380.91±0.00	380.91
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	514.48±618.79	1028.96
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	569.87±216.09	1709.60
	Paracetamol	12	1770.7±915.273	21248.44
	Pethidine	1	212.4±0.00	212.40
	Propoxyphene	1	727.16±0.00	727.16
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	503.79±0.00	503.79
	Tramadol	4	941.39±226.86	3765.58
Morphine sulphane	Morphine sulphane	2	600.51±659.86	1201.01
Morphine/ Papaveratum/Codeine	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	1548.96±399.15	4646.88
Orphenadrine 35mg/Paracetamol 450mg	Orphenadrine 35mg/Paracetamol 450mg	2	62.09±25.97	124.17
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	54.67±0.00	54.67
	Paracetamol 500mg/Codeine phosphate 10mg	7	45.83±17.83	320.80
	Paracetamol 500mg/Codeine phosphate 20mg	2	75.63±30.43	151.27
	Paracetamol 500mg/Codeine phosphate 8mg	4	86.43±46.36	345.70
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	40	80.41±32.24	3216.26
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	160	62.58±36.76	10013.51
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	17	88.58±28.38	1505.93

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Orphenadrine 35mg/Paracetamol 450mg (continued)	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	8	100.69±28.77	805.55
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	80.14±0.00	80.14
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	61.55±11.34	184.65
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	42	177.48±12..17	7454.10
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	130	80.40±50.51	10452.56
	Paracetamol 500mg/ Mephenesin 150mg	11	72.98±25.65	802.74
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	2	63.24±17.60	126.47
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	42.81±0.00	42.81
	Paracetamol	36	52.53±31.64	1891.25
	Pethidine	2	37.76±2.70	75.52
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	129.11±0.00	129.11
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	126.26±0.00	126.26
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	10	145.80±50.13	1458.03
	Propoxyphene	3	254.78±188.72	764.33
	Paracetamol 325mg/Tramadol HCL 37.5mg	45	89.46±43.73	4025.83
	Tramadol	55	179.54±173.89	9874.87
Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	Paracetamol 500mg/Codeine phosphate 8mg	2	69.13±36.38	138.25
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	82.82±0.00	82.82
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	89.02±94.25	445.11
	Paracetamol 500mg/ Mephenesin 150mg	2	40.48±18.75	80.96
	Paracetamol	5	57.89±33.13	289.46
Paracetamol 320mg/Codeine phosphate 8mg	Paracetamol 500mg/Codeine phosphate 8mg	1	45.31±0.00	45.31

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 320mg/Codeine phosphate 8mg (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	37.68±0.00	37.68
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	43.34±13.31	130.01
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	57.99±0.00	57.99
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	24.44±0.00	24.44
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	77.02±0.00	77.02
Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 500mg/Codeine phosphate 20mg	1	25.50±0.00	225.50
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	5	145.81±70.38	729.03
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	42.78±0.00	42.78
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	51.69±4.60	103.38
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	6	46.14±50.71	276.84
	Paracetamol 500mg/ Mephenesin 150mg	2	52.25±11.41	104.50
	Paracetamol	5	18.38±9.99	91.92
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	113.20±89.66	226.40
	Tramadol	3	112.19±93.69	336.58
Paracetamol 500mg/Codeine phosphate 20mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	125.10±39.17	250.20
	Paracetamol 500mg/ Mephenesin 150mg	3	87.35±17.81	262.05
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	72.94±0.00	72.94
	Paracetamol	1	40.62±0.00	40.62
	Propoxyphene	1	42.93±0.00	142.93
	Tramadol	6	146.52±63.24	897.12
Paracetamol 500mg/Codeine phosphate 8mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	76.54±0.00	76.54

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 500mg/Codeine phosphate 8mg (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	9	39.17±18.68	352.53
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	83.07±19.54	166.13
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	72.58±36.69	362.88
	Paracetamol 500mg/ Mephenesin 150mg	1	38.30±0.00	38.30
	Paracetamol	5	37.95±9.82	189.77
	Paracetamol/Codeine phosphate/Caffeine	4	100.56±53.13	402.24
	Tramadol	12	107.21±71.59	1286.54
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	190.40±0.00	190.40
	Paracetamol	1	36.68±0.00	36.68
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	140.02±0.00	280.04
	Tramadol	1	338.64±0.00	338.64
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	16	233.07±78.71	3729.13
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	142.59±0.00	142.59
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	306.19±0.00	612.38
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	43.54±0.00	43.54
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	9	173.64±84.78	1562.80
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	11	164.61±97.70	1810.68
	Paracetamol 500mg/ Mephenesin 150mg	3	171.26±26.77	513.77
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	6	397.18±56.89	2383.06
	Paracetamol	5	130.99±63.80	654.93
	Pentazocine	1	253.68±0.00	253.68
	Pethidine	3	114.34±46.59	343.02
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	5	176.49±75.52	882.46
	Propoxyphene	3	155.24±44.60	465.73

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg (continued)	Tilidine	2	286.69±28.65	773.38
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	267.05±236.04	1068.19
	Tramadol	19	285.67±120.90	5427.67
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	39	75.07±53.21	2927.70
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	8	82.19±41.72	657.48
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	74.30±4.67	148.61
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	10	47.23±30.86	472.31
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6	47.26±29.47	283.54
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	64	179.18±126.60	11467.63
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	41	50.32±45.87	2063.11
	Paracetamol 500mg/ Mephenesin 150mg	38	51.64±26.16	1962.34
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	53.47±0.00	53.47
	Paracetamol	89	35.67±34.87	3174.47
	Pethidine	4	100.93±94.08	403.72
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	6	188.87±128.06	1133.20
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	7	59.72±15.15	418.03
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	25	157.16±147.23	3928.92
	Propoxyphene	5	349.75±329.83	1748.75
	Tilidine	4	270.37±115.77	1081.47
	Paracetamol 325mg/Tramadol HCL 37.5mg	56	102.99±59.68	5767.25
	Tramadol	252	145.22±150.23	36596.12
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	2	95.84±0.01	191.67

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg (continued)	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	5	71.68±69.64	358.40
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	14	142.21±89.00	1990.99
	Paracetamol 500mg/ Mephenesin 150mg	13	84.83±55.30	1102.82
	Paracetamol	19	33.80±29.49	642.17
	Pethidine	1	51.38±0.00	51.38
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	14	55.89±33.62	782.41
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	180.91±150.65	361.81
	Tramadol	7	179.91±96.10	1259.40
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	131.79±123.72	263.57
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	439.51±61.26	1758.02
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	51.79±0.00	51.79
	Paracetamol 500mg/ Mephenesin 150mg	4	106.96±86.10	427.84
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	7	173.90±76.29	1217.31
	Tilidine	1	79.98±0.00	79.98
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	83.33±0.00	83.33
	Tramadol	22	113.28±52.52	2492.22
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	174.28±0.00	174.28
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	12	69.45±32.36	833.34
	Paracetamol 500mg/ Mephenesin 150mg	5	77.23±22.79	386.16
	Paracetamol	7	33.21±36.20	232.47
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	68.23±0.00	68.23
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	89.09±0.00	89.09
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	78.59±16.43	157.18
	Tramadol	1	67.79±0.00	67.79
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6	70.07±31.81	420.40

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg (continued)	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	109.08±0.00	109.08
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	50	71.68±48.20	3583.86
	Paracetamol 500mg/ Mephenesin 150mg	5	58.68±26.28	293.41
	Paracetamol	269	55.45±30.67	14914.84
	Tilidine	4	137.08±101.95	548.32
	Paracetamol 325mg/Tramadol HCL 37.5mg	5	114.10±29.35	570.50
	Tramadol	3	410.66±222.19	1231.99
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	15	200.30±102.35	3004.48
	Paracetamol 500mg/ Mephenesin 150mg	3	76.63±0.00	229.89
	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	82.18±0.00	82.18
	Paracetamol	12	123.41±52.05	1480.94
	Pethidine	4	215.01±130.87	860.02
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	340.44±242.52	680.88
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	12	306.88±226.08	3682.54
	Tilidine	4	249.46±141.89	997.82
	Paracetamol 325mg/Tramadol HCL 37.5mg	25	211.63±113.11	5290.67
	Tramadol	87	311.07±201.07	27063.13
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	53	77.57±54.05	411.12
	Paracetamol 500mg/ Mephenesin 150mg	68	76.89±42.39	5228.58
	Paracetamol	107	55.04±38.19	5888.95
	Paracetamol/Codeine phosphate/Caffeine	2	89.62±10.48	179.24
	Pethidine	2	33.01±12.07	66.01
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	6	310.27±155.82	1861.61
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	3	53.13±3.23	159.38
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	4	109.31±35.64	437.22
	Propoxyphene	2	98.06±15.52	196.11
	Paracetamol 325mg/Tramadol HCL 37.5mg	10	103.57±36.88	1035.68
	Tramadol	37	220.044±224.48	8141.61

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	23	48.15±25.82	1107.50
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	4	180.96±136.96	720.15
	Propoxyphene	1	169.82±0.00	169.82
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	82.46±67.13	164.92
	Tramadol	8	189.04±197.09	1512.34
Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	106.00±0.00	106.00
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	127.21±0.00	127.21
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	89.23±0.00	89.23
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	56.13±0.00	56.13
	Tramadol	4	114.97±123.18	459.87
Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	Tramadol	1	56.74±0.00	56.74
Paracetamol	Paracetamol	138	50.52±26.82	6971.42
	Pethidine	1	23.46±0.00	23.46
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	3	279.74±242.52	839.23
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	2	77.61±30.96	155.22
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	8	123.14±36.54	985.10
	Propoxyphene	4	134.14±89.79	536.57
	Tilidine	3	176.32±7.58	528.95
	Paracetamol 325mg/Tramadol HCL 37.5mg	15	133.78±78.72	2003.77
	Tramadol	96	201.21±175.53	19316.32
Paracetamol/Codeine phosphate/Caffeine	Propoxyphene HCl 50mg/ Paracetamol 325mg/	2	150.97±18.29	301.94
	Tramadol	1	187.81±0.00	187.81
Pentazocine	Paracetamol 325mg/Tramadol HCL 37.5mg	1	96.93±0.00	93.93
Pethidine	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	255.27±0.00	255.27
	Tramadol	6	250.31±289.06	1501.84
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	4	237.74±159.50	950.94
Propoxyphene HCl 50mg/ Paracetamol 325mg/	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	137.09±0.00	137.09
	Paracetamol 325mg/Tramadol HCL 37.5mg	3	190.97±63.14	572.92
	Tramadol	2	388.05±189.53	776.09

Table B1 Utilisation of two analgesic agents in combination for the year 2004.

Agents in combination		Number of Rx	Average cost	Total cost
Propoxyphene HCl 65mg/ Paracetamol 250mg/	Tilidine	3	292.95±220.45	878.84
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	248.02±82.53	496.04
	Tramadol	30	341.13±205.55	10233.75
Propoxyphene	Tramadol	4	462.00±296.59	1847.99
Tilidine	Tilidine	1	278.91±0.00	278.91
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	401.61±128.13	1606.43
	Tramadol	4	232.40±117.97	929.60
Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	31	258.52±179.85	8014.06
Tramadol	Tramadol	42	309.28±179.85	12989.62

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin/Caffeine	Ibuprofen 200mg/Paracetamol 250mg	1	107.16±0.00	107.16
Aspirin 500mg/Codeine 500mg	Aspirin 500mg/Codeine 8mg	1	48.44±0.00	48.44
	Aspirin 500mg/Codeine 8mg	1	48.75±0.00	48.75
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	1	91.06±0.00	91.06
	Ibuprofen 200mg/Paracetamol 250mg	7	64.81±43.84	453.64
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	12	118.93±66.66	1427.14
	Mefenamic acid	1	127.6±0.00	127.60
	Orphenadrine 35mg/Paracetamol 450mg	7	123.88±35.26	867.16
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	7	42.98±48.25	300.83
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	55.42±42.06	110.84
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	80.94±0.00	80.94
	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	66	80.70±37.32	5326.18
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	151.66±0.00	151.66
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Paracetamol 450mg/ Codeine phosphate 10mg	9	65.47±27.00	589.19
	Paracetamol 500mg/ Mephenesin 150mg	3	36.18±4.70	108.54
	Paracetamol	5	31.07±13.70	155.34
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Ibuprofen 400mg/ Paracetamol 325mg	1	108.141±0.00	108.11
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	5	171.56±0.00	857.80
	Ibuprofen 200mg/Paracetamol 250mg	1	68.50±0.00	68.50
	Ibuprofen 200mg/Paracetamol 350mg	1	106.98±0.00	106.98
	Ketorolac Thomethane	2	63.52±0.00	127.04
	Orphenadrine 35mg/Paracetamol 450mg	2	56.41±0.00	112.82

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	72.68±0.00	72.68
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	5	173.90±0.00	869.50
	Tramadol	2	48.77±0.00	97.54
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Ibuprofen 200mg/Paracetamol 250mg	1	83.56±0.00	83.56
	Ibuprofen 400mg/ Paracetamol 325mg	1	84.78±0.00	84.78
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	13	86.48±13.74	1124.30
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	7	99.45±16.62	696.14
	Ketorolac Thomethane	1	286.87±0.00	286.87
	Mefenamic acid	3	71.93±11.65	215.78
	Orphenadrine 35mg/Paracetamol 450mg	2	93.75±0.00	187.50
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	151.38±0.00	302.76
	Tramadol	1	81.01±0.00	81.01
Aspirin	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	5	146.05±26.05	730.27
	Ibuprofen 200mg/Paracetamol 250mg	8	65.39±38.45	523.10
	Ibuprofen 200mg/Paracetamol 350mg	2	50.46±27.25	100.92
	Ibuprofen 400mg/ Paracetamol 325mg	2	68.73±0.00	137.46
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	40	68.66±19.06	2746.51
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	18	64.62±29.62	1163.08
	Ibuprofen	2	25.99±5.88	51.98
	Mefenamic acid	10	60.28±44.70	602.83
	Orphenadrine 35mg/Paracetamol 450mg	8	54.89±23.63	439.12
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	2	42.77±24.57	85.54
	Paracetamol 500mg/Codeine phosphate 10mg	2	31.64±13.21	63.28
	Paracetamol 500mg/Codeine phosphate 8mg	3	28.66±6.70	85.97
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	49.37±0.00	49.37

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	39	31.93±29.23	1245.26
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	60.73±46.44	242.93
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	72.1±0.00	72.10
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6	42.02±18.55	252.10
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	257.48±259.70	772.45
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	27	64.51±36.36	1741.71
	Paracetamol 500mg/ Mephenesin 150mg	1	60.68±0.00	60.68
	Paracetamol	52	32.12±23.11	1370.32
	Paracetamol/Codeine phosphate/Caffeine	2	88.84±18.83	177.67
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	102.89±34.74	205.79
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	98.09±39.72	392.35
	Tramadol	7	257.59±229.17	1803.11
Buprenorphine	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	3	371.94±91.40	1115.81
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	119.27±0.00	119.27
	Morphine	1	1005.21±0.00	1005.21
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	126.48±231.16	979.43
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	3	966.35±627.67	2899.05
	Tilidine	2	379.15±423.44	758.30
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	466.04±263.30	1864.17
Codeine	Fentanyl	1	1428.2±0.00	1428.20
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	3	123.93±59.04	371.80
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	4	88.32±40.11	353.29
	Mefenamic acid	1	121.4±0.00	121.40

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Codeine (continued)	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	99.64±0.00	99.64
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	241.75±0.00	241.75
	Paracetamol	2	25.01±15.61	50.03
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	106.61±141.97	213.22
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Dihydrocodeine tartrate	4	136.41±12.22	545.65
	Dipanone HCl/Cyclizine	1	303.26±0.00	303.26
	Fentanyl	9	768.84±265.13	6919.59
	Ibuprofen 200mg/Paracetamol 250mg	11	225.47±97.57	2480.21
	Ibuprofen 200mg/Paracetamol 350mg	1	222.59±0.00	222.59
	Ibuprofen 400mg/ Paracetamol 325mg	11	137.21±77.20	1509.33
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	116	210.46±108.88	24412.81
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	33	191.74±108.62	6327.40
	Ibuprofen	6	176.30±133.63	1057.79
	Ketorolac Thomethane	3	265.36±93.19	796.09
	Mefenamic acid	7	130.19±39.08	911.33
	Morphine	6	1006.73±236.18	6040.37
	Morphine sulphate	1	104.09±0.00	104.09
	Orphenadrine 35mg/Paracetamol 450mg	31	139.93±57.43	4337.81
	Paracetamol 500mg/Codeine phosphate 8mg	1	203.72±0.00	203.72
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	20	324.07±157.58	6481.43
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	36	159.36±103.32	5736.91
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	3	111.13±18.39	33.40
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	194.31±130.66	388.62
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	21	256.89±182.00	5415.75

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	6	337.68±212.30	2026.10
	Paracetamol 500mg/ Mephenesin 150mg	2	94.35±0.00	188.70
	Paracetamol	9	223.96±139.39	2015.61
	Pethidine	6	135.43±29.04	812.57
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	219.93±0.00	439.86
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	6	571.14±0.00	3426.84
	Propoxyphene	1	287.65±0.00	287.65
	Tilidine	2	301.40±39.54	602.80
	Paracetamol 325mg/Tramadol HCL 37.5mg	14	209.77±161.09	2936.79
	Tramadol	58	485.71±274.97	28170.96
Dihydrocodeine tartrate	Dipanone HCl/Cyclizine	1	86.50±0.00	86.50
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	2	231.17±14.54	462.34
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	1	117.86±0.00	117.86
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	135.93±28.57	271.86
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	8	188.4±89.01	1507.20
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	225.64±0.00	225.64
	Tramadol	1	298.72±0.00	298.72
Fentanyl	Fentanyl	9	1785.19±532.63	16066.67
	Ibuprofen 200mg/Paracetamol 250mg	1	1875.64±0.00	1875.64
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	4	477.21±223.60	1908.85
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	1	935.5±0.00	935.50
	Mefenamic acid	1	540.64±0.00	540.64
	Morphine sulphate	1	1668.47±0.00	1668.47
	Orphenadrine 35mg/Paracetamol 450mg	5	589.48±23.96	2947.39
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	3	529.88±97.56	1589.63

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Fentanyl (continued)	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	592.34±0.00	1184.68
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	592.48±78.61	2369.93
	Paracetamol	4	538.99±1.25	2155.97
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	299.35±0.00	299.35
	Tilidine	1	1018.17±0.00	1018.17
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	776.63±0.00	776.63
	Tramadol	5	1273.87±232.92	6369.35
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg	12	89.34±22.73	1072.07
	Ibuprofen 200mg/Paracetamol 350mg	2	70.46±38.34	140.92
	Ibuprofen 400mg/ Paracetamol 325mg	1	82.65±0.00	82.65
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	25	107.99±32.92	2699.77
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	7	88.17±15.17	617.22
	Ibuprofen	5	72.00±25.26	360.00
	Ibuprofen 200mg/Codeine phosphate 10mg	8	76.87±18.57	614.96
	Mefenamic acid	100	81.52±23.12	8152.42
	Morphine	1	633.361±0.00	633.36
	Orphenadrine 35mg/Paracetamol 450mg	105	82.28±28.82	8639.29
	Paracetamol 320mg/Codeine phosphate 10mg	1	54.48±0.00	54.48
	Paracetamol 500mg/Codeine phosphate 10mg	2	38.51±12.58	77.01
	Paracetamol 500mg/Codeine phosphate 8mg	3	81.51±46.07	244.53
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	80.25±0.00	80.25
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	120.23±0.00	120.23
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	34	71.63±29.48	2435.32
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	19	75.55±36.92	1435.46

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg (continued)	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	83.97±10.22	167.93
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	47.49±0.00	47.49
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	59	58.58±19.84	3456.36
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	7	142.08±86.71	994.50
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	117	86.75±44.87	10149.78
	Paracetamol 500mg/ Mephenesin 150mg	31	66.42±16.23	2059.19
	Paracetamol	142	75.82±10766.01	10766.01
	Paracetamol/Codeine phosphate/Caffeine	1	116.91±0.00	116.91
	Pethidine	2	50.83±10.22	101.66
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	143.52±143.52	143.52
	Propoxyphene HCl 50mg/ Paracetamol 250mg/	2	114.40±69.79	228.80
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	101.19±202.38	202.38
	Propoxyphene	1	275.68±275.68	275.68
	Tilidine	1	286.73±0.00	286.73
	Paracetamol 325mg/Tramadol HCL 37.5mg	4	79.24±5.93	316.96
	Tramadol	48	333.86±266.08	16025.32
Ibuprofen 200mg/Paracetamol 350mg	Ibuprofen	6	69.83±19.86	418.97
	Ibuprofen 200mg/Codeine phosphate 10mg	2	68.71±22.54	137.42
	Mefenamic acid	2	66.34±34.66	132.68
	Orphenadrine 35mg/Paracetamol 450mg	16	65.06±12.27	1040.88
	Paracetamol 500mg/Codeine phosphate 10mg	2	48.54±11.21	97.08
	Paracetamol 500mg/Codeine phosphate 8mg	2	35.53±13.31	71.06
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	66.01±198.03	198.03
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	26	63.24±22.84	1644.16
	Paracetamol 500mg/ Mephenesin 150mg	2	53.06±15.44	106.12
	Paracetamol	9	44.39±17.63	399.56

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg (continued)	Paracetamol/Codeine phosphate/Caffeine	1	112.11±0.00	112.11
	Tramadol	5	93.09±37.21	480.46
Ibuprofen 400mg/ Paracetamol 325mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	91.11±0.00	91.11
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	3	102.84±308.52	308.52
	Ibuprofen	1	52.90±0.00	52.90
	Mefenamic acid	8	100.02±38.36	800.18
	Orphenadrine 35mg/Paracetamol 450mg	44	112.71±82.50	4959.36
	Paracetamol 500mg/Codeine phosphate 10mg	2	66.63±1.78	133.26
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	17	239.68±81.87	4074.54
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	14	68.25±34.57	955.49
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	3	131.88±0.00	395.64
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	7	155.14±88.53	1086.01
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	75.65±20.04	302.58
	Paracetamol 500mg/ Mephenesin 150mg	6	82.99±18.59	497.93
	Paracetamol 400mg/ Codeine phosphate 8mg/Meprobamate 200mg	3	58.87±11.30	176.60
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	112.42±0.00	112.42
	Paracetamol	2	144.95±103.13	289.89
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	169.38±0.00	169.38
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	122.42±0.00	122.42
	Paracetamol 325mg/Tramadol HCL 37.5mg	12	124.99±44.33	1499.86
	Tramadol	9	191.39±89.47	1722.55
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	19	129.48±64.00	2460.12
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	26	104.39±37.64	2714.12
	Ibuprofen	18	118.69±55.50	2136.34

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Ibuprofen 200mg/Codeine phosphate 10mg	1	85.56±0.00	85.56
	Ketorolac Thomethane	4	153.81±79.75	615.23
	Mefenamic acid	201	93.60±33.08	18813.24
	Morphine	2	161.09±66.55	322.18
	Morphine sulphate	1	49.55±0.00	49.55
	Orphenadrine 35mg/Paracetamol 450mg	274	93.04±35.41	25493.46
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	120.27±0.00	120.27
	Paracetamol 320mg/Codeine phosphate 8mg	3	51.08±5.12	153.25
	Paracetamol 500mg/Codeine phosphate 10mg	3	65.76±13.27	197.27
	Paracetamol 500mg/Codeine phosphate 20mg	1	88.20±0.00	88.20
	Paracetamol 500mg/Codeine phosphate 8mg	22	92.10±24.54	2026.22
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	2	108.55±23.93	217.10
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	40	118.19±43.78	4727.76
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	342	93.39±49.32	31598.65
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	7	84.61±41.35	592.28
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	5	174.19±143.05	870.93
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	6	67.18±23.50	403.06
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	61	77.95±25.77	4754.79
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	167	184.72±101.67	30848.86
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	217	89.07±43.69	19327.31
	Paracetamol 500mg/ Mephenesin 150mg	29	74.55±44.95	2161.96
	Paracetamol 400mg/ Codeine phosphate 8mg/Meprobamate 200mg	3	77.84±26.82	233.53
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	2	78.96±7.28	157.91

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Paracetamol	189	89.49±33.79	16914.01
	Paracetamol/Codeine phosphate/Caffeine	2	115.27±0.00	230.54
	Pethidine	5	63.54±15.56	317.72
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	6	178.78±51.30	1072.68
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	2	86.69±7.36	173.37
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	13	139.12±38.00	1808.60
	Propoxyphene	1	220.55±0.00	220.55
	Tilidine	8	146.77±104.93	1174.19
	Paracetamol 325mg/Tramadol HCL 37.5mg	43	160.18±95.77	688.89
	Tramadol	349	283.69±189.81	99006.15
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Ibuprofen	6	78.19±25.48	469.16
	Ketorolac Thomethane	6	96.06±59.13	576.35
	Mefenamic acid	35	80.31±26.82	2810.49
	Orphenadrine 35mg/Paracetamol 450mg	318	72.48±17.72	23048.49
	Paracetamol 320mg/Codeine phosphate 8mg	3	47.02±7.03	141.07
	Paracetamol 500mg/Codeine phosphate 10mg	3	66.74±4.60	200.23
	Paracetamol 500mg/Codeine phosphate 8mg	8	74.03±32.31	592.20
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	59.72±0.00	59.72
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	24	104.56±38.83	2504.61
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	215	61.37±26.67	13195.32
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	5	67.37±336.85	336.85
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	3	101.54±25.95	304.61
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	2	48.43±1.22	96.85
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	12	74.40±22.50	892.81
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	100	145.52±64.82	14551.50

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	89	83.79±48.43	7457.10
	Paracetamol 500mg/ Mephenesin 150mg	19	61.04±12.11	1159.71
	Paracetamol	42	64.53±32.50	2710.08
	Paracetamol/Codeine phosphate/Caffeine	1	166.96±0.00	166.96
	Pethidine	3	54.02±8.63	162.06
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	196.33±0.00	196.33
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	6	90.72±22.73	544.36
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	114.12±26.06	228.24
	Tilidine	1	157.60±0.00	157.60
	Paracetamol 325mg/Tramadol HCL 37.5mg	29	102.37±31.34	2968.80
	Tramadol	174	250.87±190.43	43651.60
Ibuprofen	Ibuprofen	2	86.21±23.82	172.41
	Mefenamic acid	11	54.4±27.94	598.40
	Orphenadrine 35mg/Paracetamol 450mg	19	572.24±26.98	1087.58
	Paracetamol 320mg/Codeine phosphate 8mg	5	15.95±0.00	79.75
	Paracetamol 500mg/Codeine phosphate 10mg	5	11.58±4.38	57.93
	Paracetamol 500mg/Codeine phosphate 20mg	1	51.76±0.00	51.76
	Paracetamol 500mg/Codeine phosphate 8mg	7	24.95±19.08	174.68
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	25.93±0.00	25.93
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	112	19.16±7.37	2145.62
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	60.56±40.31	121.13
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	61	36.6±24.69	2232.81
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	140.12±104.57	420.37
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	27	48.77±41.25	1316.78
	Paracetamol 500mg/ Mephenesin 150mg	11	46.52±15.86	511.74
	Paracetamol	122	31.15±20.75	3799.74
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	71.15±0.00	71.15

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen (continued)	Tilidine	2	62.28±3.83	124.55
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	47.44±0.00	47.44
	Tramadol	1	58.78±0.00	58.78
Ibuprofen 200mg/Codeine phosphate 10mg	Mefenamic acid	1	54.72±0.00	54.72
	Orphenadrine 35mg/Paracetamol 450mg	17	56.42±12.70	959.21
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	49.49±16.01	98.98
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	51.94±9.05	155.84
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	20	56.79±20.52	1135.76
	Paracetamol 500mg/ Mephenesin 150mg	6	48.10±11.43	288.62
	Paracetamol	11	52.33±18.90	575.58
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	154.83±0.00	154.83
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	74.93±0.00	74.93
Ketorolac Tromethane	Mefenamic acid	2	42.25±0.00	84.5
	Orphenadrine 35mg/Paracetamol 450mg	1	281.33±0.00	281.33
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	92.04±0.00	184.08
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	10	149.8±46.57	1498.01
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	12	209.09±90.89	2509.02
	Paracetamol 500mg/ Mephenesin 150mg	1	189.68±0.00	189.68
	Paracetamol	1	82.61±0.00	82.61
	Pethidine	1	38.01±0.00	38.01
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	120.39±0.00	120.39
	Tramadol	9	103.36±170.64	930.28
Mefenamic Acid	Mefenamic acid	47	68.04±25.90	3197.84
	Orphenadrine 35mg/Paracetamol 450mg	39	86.7±71.22	3381.12
	Paracetamol 500mg/Codeine phosphate 10mg	7	26.41±10.45	184.86
	Paracetamol 500mg/Codeine phosphate 20mg	1	126.2±0.00	126.2
	Paracetamol 500mg/Codeine phosphate 8mg	7	63.67±19.58	445.68
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	6	139.38±53.99	836.3

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Mefenamic Acid (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	146	50.76±27.23	7411.17
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	5	31.99±12.05	159.96
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	4	69.12±4.78	276.48
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	2	17.98±3.27	35.95
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	353	44.24±23.41	15617.43
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	15	127.33±94.74	1909.98
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	59	54.15±31.80	3194.86
	Paracetamol 500mg/ Mephenesin 150mg	14	40.32±11.53	564.52
	Paracetamol 400mg/ Codeine phosphate 8mg/Meprobamate 200mg	1	38.92±0.00	38.92
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	2	30.17±1.36	60.34
	Paracetamol	735	51.49±27.54	37845.6
	Pethidine	1	34.00±0.00	34
	Tilidine	5	164.80±88.11	824.02
	Paracetamol 325mg/Tramadol HCL 37.5mg	16	99.61±52.48	1593.76
	Tramadol	20	127.98±91.14	2559.66
Morphine	Morphine sulphate	2	299.76±133.47	599.52
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	8	202.08±96.22	1616.6
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	485.49±308.45	1456.46
	Paracetamol	6	1658.79±19.84	9952.75
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	1074.43±0.00	1074.43
Morphine sulphate	Tramadol	1	111.73±0.00	111.73
Morphine/Papaveratum/Codeine	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	6	1805.95±40.06	10835.67

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	46.43±0.00	46.43
	Paracetamol 500mg/Codeine phosphate 10mg	12	45.01±12.49	540.1
	Paracetamol 500mg/Codeine phosphate 8mg	4	57.13±19.68	228.51
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	2	58.62±0.01	117.25
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	31	86.34±36.63	2676.4
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	125	54.00±26.85	6750.6
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	10	61.99±23.13	619.92
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	111.98±17.85	223.97
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	33.46±0.00	33.46
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	5	45.22±4.96	226.11
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	42	123.41±36.07	5183.35
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	150	58.23±27.54	8734.58
	Paracetamol 500mg/ Mephenesin 150mg	31	51.29±16.22	1589.85
	Paracetamol 400mg/ Codeine phosphate 8mg/Meprobamate 200mg	1	52.46±0.00	52.46
	Paracetamol	34	42.70±17.04	1451.95
	Paracetamol/Codeine phosphate/Caffeine	1	102.08±0.00	102.08
	Pethidine	1	35.85±0.00	35.85
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	3	319.58±165.99	958.73
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	2	154.65±68.01	309.3
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	3	119.54±13.99	358.61
	Paracetamol 325mg/Tramadol HCL 37.5mg	52	78.89±25.73	4102.51
	Tramadol	88	163.77±136.77	14411.98
Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	Paracetamol	3	45.16±23.43	135.49

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 320mg/Codeine phosphate 8mg	Paracetamol 500mg/Codeine phosphate 8mg	1	22.76±0.00	22.76
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	24.24±0.00	48.48
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	28.74±0.00	28.74
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	42.03±5.95	126.08
	Paracetamol	1	16.00±0.00	16
Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	50.32±36.75	100.63
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	33.10±28.48	66.2
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	25.12±5.14	75.36
	Paracetamol	5	18.13±11.43	90.14
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	80.25±8.65	160.5
	Tramadol	5	112.67±29.08	563.35
Paracetamol 500mg/Codeine phosphate 20mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	233.81±17.21	467.62
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	80.44±0.00	80.44
	Paracetamol	1	69.80±0.00	69.8
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	94.44±0.00	94.44
Paracetamol 500mg/Codeine phosphate 8mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	69.48±0.00	69.48
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	33.77±0.00	33.77
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	73.02±23.68	219.05
	Paracetamol 500mg/ Mephenesin 150mg	1	73.87±0.00	73.87
	Paracetamol	1	67.29±0.00	67.29
	Tramadol	7	193.71±181.59	1335.94
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Paracetamol	1	31.27±0.00	31.27
	Tramadol	1	181.55±0.00	181.55

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	3	99.23±64.43	297.77
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	51.49±0.00	51.49
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	10	249.45±127.20	2494.54
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	103.89±109.00	415.56
	Paracetamol	1	30.18±0.00	30.18
	Pethidine	10	93.94±30.16	939.44
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	132.10±0.00	132.1
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	153.95±0.00	153.95
	Propoxyphene	2	109.39±0.00	218.78
	Tilidine	2	164.68±115.74	329.36
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	112.65±0.00	225.3
	Tramadol	13	183.43±0.00	2384.63
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	10	58.89±3.66	588.94
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	20.45±0.00	80.18
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	12.39±0.00	57.55
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	2	57.71±37.87	24.78
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	9	155.80±100.26	519.38
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	62	57.38±48.56	9659.37
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	29	36.35±8.94	1663.94
	Paracetamol 500mg/ Mephenesin 150mg	18	33.61±6.86	654.26
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	4	25.50±20.84	134.44

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg (continued)	Paracetamol	43	25.09±12.64	1096.38
	Pethidine	11	204.54±43.56	276.01
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	47.18±0.00	409.08
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	114.66±58.99	47.18
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	11	114.66±58.98	1261.25
	Propoxyphene	3	97.63±19.78	292.88
	Paracetamol 325mg/Tramadol HCL 37.5mg	45	109.66±51.32	4934.51
	Tramadol	166	180.52±240.39	29966.33
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	6	72.01±50.36	432.05
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	84.68±18.34	254.03
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	61.29±19.86	306.45
	Paracetamol 500mg/ Mephenesin 150mg	2	87.29±31.01	174.57
	Paracetamol	8	45.55±32.42	364.4
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	26.59±0.00	26.59
	Tramadol	1	76.58±0.00	76.58
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	419.58±58.98	1678.29
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	184.34±29.88	553.01
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	178.56±94.14	357.12
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	33.07±0.00	33.07
	Tramadol	3	124.68±47.21	374.05
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	14.22±0.00	14.22
	Paracetamol 500mg/ Mephenesin 150mg	1	21.69±0.00	21.69
	Paracetamol	3	24.30±16.02	72.89
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	18.61±2.31	55.82
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	123.07±13.77	369.2
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	49	53.37±31.14	2615.3

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg (continued)	Paracetamol 500mg/ Mephenesin 150mg	2	27.55±0.38	55.11
	Paracetamol	185	48.46±23.58	8965.25
	Tilidine	2	153.36±0.00	306.72
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	94.41±0.00	188.82
	Tramadol	4	223.04±69.25	892.16
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	15	162.82±114.13	2442.32
	Paracetamol 500mg/ Mephenesin 150mg	7	92.32±15.08	646.25
	Paracetamol	7	110.28±52.90	771.94
	Pethidine	2	103.06±1.82	206.11
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	148.49±0.00	148.49
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	5	199.41±43.03	992.06
	Tilidine	2	162.20±78.63	324.4
	Paracetamol 325mg/Tramadol HCL 37.5mg	38	169.87±93.19	6455.24
	Tramadol	59	257.46±150.09	15189.9
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	53	70.66±49.50	3745.17
	Paracetamol 500mg/ Mephenesin 150mg	52	59.48±27.59	3092.78
	Paracetamol	87	42.45±31.33	3692.97
	Paracetamol/Codeine phosphate/Caffeine	1	82.21±0.00	82.21
	Pethidine	7	29.53±15.66	206.68
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	6	230.18±23.05	1381.08
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	7	82.44±19.13	577.1
	Paracetamol 325mg/Tramadol HCL 37.5mg	7	66.99±22.54	468.9
	Tramadol	42	247.98±232.77	10415.22
Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	12	31.38±9.03	376.5
	Paracetamol/Codeine phosphate/Caffeine	1	114.81±0.00	114.81
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	104.15±0.00	104.15
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	37.64±16.66	75.28
	Tramadol	5	79.89±20.72	399.45

Table B 2 Utilisation of two analgesic agents in combination for the year 2005

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 400mg/ Codeine phosphate 8mg/Meprobamate 200mg	Tramadol	1	61.09±0.00	61.09
Paracetamol	Paracetamol	150	39.86±25.60	5979.29
	Pethidine	1	15.15±0.00	15.15
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	68.67±0.00	68.67
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	3	128.84±36.81	686.51
	Propoxyphene	3	236.08±1.76	789.23
	Tilidine	4	249.98±109.12	999.94
	Paracetamol 325mg/Tramadol HCL 37.5mg	7	61.38±27.58	429.66
	Tramadol	89	171.24±157.60	15240.17
Pethidine	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	7	108.5±54.52	759.49
	Tilidine	1	203.56±0.00	203.56
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	90.06±27.72	180.11
	Tramadol	13	215.2±220.24	2797.55
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Propoxyphene	1	418.75±0.00	418.75
	Tilidine	1	197.43±0.00	197.43
	Tramadol	4	350.85±250.29	1403.41
Propoxyphene HCl 50mg/ Paracetamol 325mg/	Paracetamol 325mg/Tramadol HCL 37.5mg	1	155.66±0.00	155.66
	Tramadol	1	72.57±0.00	72
Propoxyphene HCl 65mg/ Paracetamol 250mg/	Paracetamol 325mg/Tramadol HCL 37.5mg	8	173.16±58.95	57
	Tramadol	30	386.06±240.58	1385.24
Propoxyphene	Tramadol	1	308.18±0.00	308.18
Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	31	254.00±211.28	11581.72
Tramadol	Tramadol	25	148.88±126.04	7873.89

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin 500mg/Codeine 8mg	Codeine	1	396.6±0.00	396.60
	Ibuprofen 200mg/Paracetamol 350mg	1	58.98±0.00	58.98
	Orphenadrine 35mg/Paracetamol 450mg	1	116.36±0.00	116.36
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	54.66±0.00	54.66
	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	36	81.09±23.34	2919.40
	Paracetamol 450mg/ Doxylamine succinate 5mg/Caffeine 450mg/ Codeine phosphate 10mg	2	81.22±52.01	162.43
	Paracetamol	2	37.84±17.06	75.68
	Tramadol	1	119.83±0.00	119.83
Aspirin 37.5mg/ Paracetamol 325mg/ Codeine phosphate	Ibuprofen	1	19.53±0.00	19.53
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 15mg/ Caffeine 50mg	Ibuprofen	1	43.07±0.00	43.07
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	95.02±0.00	95.02
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	135.93±0.00	135.93
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Ibuprofen 400mg/ Paracetamol 325mg	1	81.13±0.00	81.13
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	315.71±0.00	315.71
	Orphenadrine 35mg/Paracetamol 450mg	1	111.30±0.00	111.30
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	63.41±20.45	126.82
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	207.48±0.00	207.48
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	200.27±0.00	200.27
	Tramadol	1	187.86±0.00	187.86
Aspirin	Aspirin	1	35.68±0.00	35.68
	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	1	213.84±0.00	213.84
	Ibuprofen 200mg/Paracetamol 250mg	11	26.67±22.13	293.45

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Aspirin (continued)	Ibuprofen 400mg/ Paracetamol 325mg	1	64.37±0.00	64.37
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	38	39.34±26.56	2634.84
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	18	17.97±37.49	1295.49
	Mefenamic acid	2	59.71±24.52	119.42
	Orphenadrine 35mg/Paracetamol 450mg	6	45.73±8.73	274.35
	Paracetamol 500mg/Codeine phosphate 10mg	2	19.11±0.32	38.21
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	44.65±0.00	44.65
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	76.53±4.53	153.06
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	9	30.52±14.20	274.68
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	65.34±9.60	130.67
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	37.31±5.92	111.92
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	14	56.69±34.43	793.67
	Paracetamol 500mg/ Mephenesin 150mg	1	53.7±0.00	53.70
	Paracetamol	17	33.64±23.45	571.81
	Paracetamol 325mg/Tramadol HCL 37.5mg	8	91.98±63.33	735.80
	Tramadol	5	298.34±47.92	1491.70
Buprenorphine	Paracetamol 500mg/Codeine phosphate 20mg	1	342.53±0.00	342.53
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	236.82±0.00	236.82
Codeine	Ibuprofen 200mg/Paracetamol 250mg	1	66.87±0.00	66.87
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	2	148.94±18.29	297.87
	Paracetamol 500mg/Codeine phosphate 20mg	1	203.04±0.00	203.04
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	205.19±51.15	410.38
	Paracetamol	1	21.83±0.00	21.83
	Tramadol	1	552.27±0.00	552.27

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Fentanyl	6	1439.01±748.69	8634.04
	Ibuprofen 200mg/Paracetamol 250mg	8	172.81±84.72	1382.49
	Ibuprofen 400mg/ Paracetamol 325mg	4	239.72±83.92	958.89
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	61	261.64±127.61	15959.80
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	11	240.02±101.90	2640.20
	Ibuprofen	1	99.68±0.00	99.68
	Ketorolac Thomethane	1	540.17±0.00	540.17
	Mefenamic acid	4	232.44±132.17	929.74
	Orphenadrine 35mg/Paracetamol 450mg	22	196.68±103.31	4327.00
	Paracetamol 500mg/Codeine phosphate 10mg	2	128.63±34.57	257.25
	Paracetamol 500mg/Codeine phosphate 8mg	1	61.05±0.00	61.05
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	22	266.35±198.30	5859.77
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	14	299.93±200.60	4198.95
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	13	320.91±192.07	4171.82
	Paracetamol 500mg/ Mephenesin 150mg	1	105.00±0.00	105.00
	Paracetamol	5	242.68±108.93	1213.42
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	534.66±0.00	534.66
	Propoxyphene	1	287.65±0.00	287.65
	Paracetamol 325mg/Tramadol HCL 37.5mg	16	321.86±269.42	5149.68
	Tramadol	46	460.00±267.66	21160.07
Fentanyl	Fentanyl	4	2531.49±0.00	10125.96
	Ibuprofen 400mg/Paracetamol 325mg	2	342.11±345.51	684.21
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	569.87±0.00	569.87
	Orphenadrine 35mg/Paracetamol 450mg	4	607.2±0.25	2428.78
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	4	860.25±720.80	3441.00
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	1071.95±0.00	1071.95
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	2238.95±0.00	2238.95

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Fentanyl (continued)	Tilidine	1	1079.09±0.00	1079.09
	Paracetamol 325mg/Tramadol HCL 37.5mg	6	1070.59±599.59	6423.56
	Tramadol	4	1989.81±1429.71	7959.22
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg	3	18.78±31.25	56.34
	Ibuprofen 200mg/Paracetamol 350mg	1	92.12±0.00	92.12
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	12	61.89±28.86	742.63
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	7	73.92±30.49	517.46
	Ibuprofen	5	40.62±25.51	203.08
	Ibuprofen 200mg/Codeine phosphate 10mg	1	42.03±0.00	42.03
	Ketorolac Thomethane	3	67.31±0.00	201.93
	Mefenamic acid	71	67.01±26.43	4758.00
	Orphenadrine 35mg/Paracetamol 450mg	74	52.50±22.20	3885.29
	Paracetamol 500mg/Codeine phosphate 10mg	2	12.4±2.71	24.80
	Paracetamol 500mg/Codeine phosphate 20mg	1	136.45±0.00	136.45
	Paracetamol 500mg/Codeine phosphate 8mg	3	68.27±44.01	204.82
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	26.04±0.00	26.04
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	12	57.19±26.99	686.24
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	8	69.63±46.68	557.04
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	28	52.20±29.07	1461.62
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	4	173.39±100.04	693.57
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	78	54.41±42.04	4243.79
	Paracetamol 500mg/ Mephenesin 150mg	10	36.38±14.49	363.83
	Paracetamol	68	65.98±34.86	4486.74
	Pethidine	4	53.48±2.65	213.91
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	111.71±0.00	111.71
	Tilidine	2	48.17±6.05	96.34
	Paracetamol 325mg/Tramadol HCL 37.5mg	8	50.2±55.11	401.57

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg (continued)	Tramadol	59	239.82±245.81	14149.65
Ibuprofen 200mg/Paracetamol 350mg	*Ibuprofen*	1	80.99±0.00	80.99
	Mefenamic acid	5	70.11±28.51	350.54
	Orphenadrine 35mg/Paracetamol 450mg	17	70.11±13.69	1191.80
	Paracetamol 500mg/Codeine phosphate 20mg	2	68.47±3.69	136.94
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	51.76±0.00	51.76
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	132.3±53.57	396.89
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	53.51±0.00	53.51
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	20	70.75±28.99	1415.09
	Paracetamol 500mg/ Mephenesin 150mg	6	56.93±7.00	341.60
	Paracetamol	4	42.50±14.34	170.09
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	102.45±0.00	102.45
	Tramadol	3	79.34±33.14	238.03
Ibuprofen 400mg/ Paracetamol 325mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	3	110.96±7.50	332.88
	Mefenamic acid	3	122.58±15.35	367.75
	Orphenadrine 35mg/Paracetamol 450mg	20	95.01±7.66	1900.20
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	10	129.34±82.00	1293.38
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	18	64.93±14.65	1168.80
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	92.25±0.00	92.25
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	11	149.74±37.29	1647.19
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	12	68.14±14.28	817.71
	Paracetamol	4	84.84±66.12	339.37
	Pethidine	1	72.75±0.00	72.75
	Paracetamol 325mg/Tramadol HCL 37.5mg	16	175.88±108.88	2814.15

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 400mg/ Paracetamol 325mg (continued)	Tramadol	14	435.02±240.44	6090.29
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	29	88.25±29.68	2558.53
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	19	106.64±39.87	2026.25
	Ibuprofen	13	101.8±42.24	1323.46
	Ketorolac Thomethane	1	226.26±0.00	226.26
	Mefenamic acid	96	78.23±26.99	7509.61
	Morphine	1	341.90±0.00	341.90
	Orphenadrine 35mg/Paracetamol 450mg	283	82.51±20.60	23351.65
	Paracetamol 500mg/Codeine phosphate 10mg	3	79.72±52.78	239.16
	Paracetamol 500mg/Codeine phosphate 8mg	3	85.48±46.63	256.44
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	14	124.32±59.96	1740.43
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	141	75.38±39.67	10628.18
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	49.78±0.00	49.78
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	100.81±13.39	201.63
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	50.47±0.00	50.47
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	20	76.32±21.15	1526.43
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	38	189.22±121.99	7190.21
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	167	75.14±29.26	12548.15
	Paracetamol 500mg/ Mephenesin 150mg	31	72.63±24.79	225.45
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	3	72.18±27.45	216.53
	Paracetamol	121	80.72±54.99	9766.74
	Paracetamol/Codeine phosphate/Caffeine	1	69.57±0.00	69.57
	Pethidine	6	56.80±5.51	340.82
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	14	200.59±110.10	2808.23

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Propoxyphene HCl 65mg/ Paracetamol 250mg/	3	138.25±46.23	414.75
	Tilidine	6	96.25±121.50	577.48
	Paracetamol 325mg/Tramadol HCL 37.5mg	49	113.87±69.60	5579.70
	Tramadol	265	234.62±170.57	62173.74
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	6	108.95±21.25	653.72
	Ibuprofen	5	87.62±5.77	438.08
	Ibuprofen 200mg/Codeine phosphate 10mg	2	243.09±195.56	486.17
	Mefenamic acid	45	84.88±29.77	3819.42
	Orphenadrine 35mg/Paracetamol 450mg	252	72.43±22.52	18253.29
	Paracetamol 500mg/Codeine phosphate 10mg	4	60.12±5.65	240.46
	Paracetamol 500mg/Codeine phosphate 20mg	7	136.24±0.00	953.68
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	75.84±0.00	75.84
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	8	85.56±11.93	684.47
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	117	74.76±38.36	8746.54
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	3	124.95±14.61	374.86
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	4	67.94±7.24	271.77
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	30	148.67±54.99	4459.96
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	89	81.2±26.29	7226.59
	Paracetamol 500mg/ Mephenesin 150mg	7	72.14±3.10	505.00
	Paracetamol	22	62.21±24.59	1368.68
	Paracetamol/Codeine phosphate/Caffeine	9	59.81±5.18	538.32
	Pethidine	1	202.02±0.00	202.02
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	3	122.99±58.96	368.96
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	26	134.78±58.56	3504.19
	Paracetamol 325mg/Tramadol HCL 37.5mg	194	254.83±178.24	49437.69
	Tramadol	7	384.03±113.07	2688.19

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ibubrofen	Ibuprofen	1	159.48±0.00	159.48
	Mefenamic acid	15	47.03±12.41	705.42
	Orphenadrine 35mg/Paracetamol 450mg	18	52.13±25.15	938.31
	Paracetamol 320mg/Codeine phosphate 8mg	1	11.17±0.00	11.17
	Paracetamol 500mg/Codeine phosphate 8mg	3	26.1±35.51	78.30
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	33	17.22±15.84	568.39
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	13.43±3.78	40.30
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	12	35.01±17.59	420.14
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	104.64±0.00	104.64
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	19	76.94±66.63	1461.96
	Paracetamol 500mg/ Mephenesin 150mg	6	47.49±13.45	284.94
	Paracetamol	53	37.56±27.72	1990.74
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	67.25±0.00	67.25
	Tramadol	4	99.41±84.96	397.64
Ibuprofen 200mg/Codeine phosphate 10mg	Mefenamic acid	1	66.50±0.00	66.50
	Orphenadrine 35mg/Paracetamol 450mg	20	65.57±10.41	1311.38
	Paracetamol 500mg/Codeine phosphate 10mg	1	43.96±0.00	43.96
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	67.67±45.79	135.33
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	56.15±1.44	112.29
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	12	63.57±19.12	762.79
	Paracetamol 500mg/ Mephenesin 150mg	9	46.56±6.87	419.07
	Paracetamol	1	66.28±0.00	66.28
Ketorolac tromethane	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	88.49±3.08	1763.98

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ketorolac tromethane (continued)	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	108.33±8.61	216.65
	Tramadol	14	106.99±161.06	1497.82
Mefenamic acid	Mefenamic acid	32	60.59±22.34	1938.84
	Orphenadrine 35mg/Paracetamol 450mg	26	102.26±92.44	2658.75
	Paracetamol 500mg/Codeine phosphate 10mg	2	22.05±4.53	44.10
	Paracetamol 500mg/Codeine phosphate 20mg	1	24.98±0.00	24.98
	Paracetamol 500mg/Codeine phosphate 8mg	6	43.29±16.79	259.71
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	1	74.63±0.00	74.63
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	73	55.85±45.97	4076.72
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	40.17±0.00	40.17
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	4	62.02±12.03	248.06
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	173	40.16±16.57	6947.35
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	22	150.38±88.92	3308.45
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	62	64.43±39.47	3994.61
	Paracetamol 500mg/ Mephenesin 150mg	6	48.2±39.51	289.22
	Paracetamol	474	54.04±26.66	25612.81
	Pethidine	1	21.73±0.00	21.73
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	102.41±0.00	102.41
	Tilidine	4	162.99±82.75	651.94
	Paracetamol 325mg/Tramadol HCL 37.5mg	20	101.31±61.65	2026.10
	Tramadol	2	57.07±6.48	114.14
Morphine	Morphine	4	1081.15±0.00	4324.60
Morphine sulphate	Orphenadrine 35mg/Paracetamol 450mg	1	35.64±0.00	35.64
	Tilidine	1	705.76±0.00	705.76
	Tramadol	1	44.44±0.00	44.44
Ketorolac tromethane	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	1884.49±13.80	5653.46

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Ketorolac tromethane (continued)	Pethidine	1	22.14±0.00	22.14
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 500mg/Codeine phosphate 10mg	8	45.57±3.80	364.52
	Paracetamol 500mg/Codeine phosphate 20mg	2	77.26±0.00	154.52
	Paracetamol 500mg/Codeine phosphate 8mg	4	66.07±16.03	264.29
	Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	2	54.43±5.95	108.85
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	21	93.93±75.54	1972.44
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	93	63.91±39.56	5943.68
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	3	62.4±25.54	187.20
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	2	125.09±6.62	250.18
	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	69.86±0.00	68.86
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	5	59.95±27.27	299.74
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	40	169.95±139.70	6797.88
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	155	64.96±25.67	10069.53
	Paracetamol 500mg/ Mephenesin 150mg	46	54.2±8.93	2493.26
	Paracetamol	37	71.8±54.97	2656.75
	Pethidine	1	41.27±0.00	41.27
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	7	164.6±74.66	1152.19
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	99.71±0.00	99.71
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	115.37±0.00	115.37
	Propoxyphene	1	181.44±0.00	181.44
	Paracetamol 325mg/Tramadol HCL 37.5mg	44	103.90±40.99	4571.63
	Tramadol	61	145.10±106.68	8850.81
Paracetamol 320mg/Codeine phosphate 8mg	Paracetamol 500mg/Codeine phosphate 8mg	1	29.15±0.00	29.15
	Paracetamol	1	31.54±0.00	31.54

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	73.26±31.31	146.52
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	263.73±204.53	527.45
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	30.5±0.00	30.50
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	14.71±0.00	14.71
	Tramadol	2	32.92±0.00	65.84
Paracetamol 500mg/Codeine phosphate 20mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	59.82±37.09	119.64
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	58.56±0.00	58.56
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	5	133.93±22.89	669.65
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	202.94±0.00	202.94
	Paracetamol	1	94.75±0.00	94.75
Paracetamol 500mg/Codeine phosphate 8mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	28.35±0.00	28.35
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	47.06±0.00	47.06
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	7	43.84±20.96	306.91
	Paracetamol 500mg/ Mephenesin 150mg	5	50.67±4.93	253.34
	Paracetamol	2	35.26±28.16	70.52
	Pethidine	1	31.54±0.00	31.54
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	74.32±0.00	74.32
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	210.01±0.00	210.01
	Tramadol	2	76.57±75.60	153.14
Paracetamol 500mg/ Codeine phosphate 8mg/ Ascorbic acid 50mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	133.39±0.00	113.39
	Tramadol	1	128.89±0.00	128.89
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	233.68±0.00	233.68
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	256.96±1.14	513.91

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg (continued)	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	6	195.21±67.22	1171.24
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	83.08±25.53	166.16
	Paracetamol 500mg/ Mephenesin 150mg	1	59.25±0.00	59.25
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	141.02±0.00	141.02
	Paracetamol 325mg/Tramadol HCL 37.5mg	1	104.85±0.00	104.85
	Tramadol	12	241.53±85.84	2898.33
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	3	58.56±18.17	175.69
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	1	55.86±0.00	55.86
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	40.24±14.49	120.71
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	18	208.1±93.48	3745.73
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	13	44.43±19.25	577.56
	Paracetamol 500mg/ Mephenesin 150mg	5	34.29±7.07	171.47
	Paracetamol 500mg/ Codeine phosphate 10mg/ Meprobamate 125mg	1	85.23±0.00	85.23
	Paracetamol	9	33.17±27.82	298.54
	Pethidine	1	22.65±0.00	22.65
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	1	2.72±0.00	2.72
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	2	262.8±77.33	525.60
	Tilidine	1	32.75±0.00	32.75
	Paracetamol 325mg/Tramadol HCL 37.5mg	20	144.41±129.81	2888.11
	Tramadol	102	261.47±227.06	26669.81
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	5	71.98±4.30	359.88
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	11	113.78±71.39	1251.60
	Paracetamol 500mg/ Mephenesin 150mg	1	83.49±0.00	83.49

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	201.03±0.00	201.30
	Tramadol	6	151.15±83.60	906.92
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	27.92±5.41	83.75
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	250.73±0.00	250.73
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	34	57.16±39.68	1943.41
	Paracetamol	110	41.87±23.94	4605.64
	Pethidine	1	21.27±0.00	21.27
	Tilidine	2	12.94±2.71	25.87
	Tramadol	1	651.59±0.00	651.59
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	218.59±24.28	437.17
	Paracetamol 500mg/ Mephenesin 150mg	3	147.32±0.00	441.96
	Paracetamol	5	69.81±39.22	349.07
	Pethidine	2	139.27±0.00	578.54
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	25.87±166.58	517.74
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	5	454.89±296.64	2274.45
	Propoxyphene	1	428.4±0.00	428.40
	Paracetamol 325mg/Tramadol HCL 37.5mg	14	298.58±170.11	4180.05
	Tramadol	21	201.98±127.42	4241.68
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	56	78.53±60.49	43.97
	Paracetamol 500mg/ Mephenesin 150mg	44	65.74±45.03	2892.54
	Paracetamol	80	51.96±39.69	4157.07
	Pethidine	1	24.58±0.00	24.58
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	13	211.54±98.33	2749.96
	Propoxyphene	1	78.45±0.00	78.45
	Tilidine	1	180.15±0.00	180.15
	Paracetamol 325mg/Tramadol HCL 37.5mg	9	86.24±37.00	776.12
	Tramadol	43	296.3±247.67	12766.55

Table B 3 Utilisation of two analgesics in combination for the year 2006

Agents in combination		Number of Rx	Average cost	Total cost
Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	8	50.74±33.67	405.92
	Propoxyphene HCl 50mg/ Paracetamol 325mg	1	115.93±0.00	115.93
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	104.15±0.00	104.15
	Paracetamol 325mg/Tramadol HCL 37.5mg	2	119.05±32.81	238.10
Paracetamol	Paracetamol	56	33.09±26.48	1853.27
	Pethidine	1	71.52±0.00	71.52
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	101.47±1.18	202.93
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	31.95±0.00	31.95
	Propoxyphene	1	122.17±0.00	122.17
	Tilidine	4	65.57±113.37	262.26
	Paracetamol 325mg/Tramadol HCL 37.5mg	15	110.75±90.74	1661.32
	Tramadol	49	197.44±148.44	9674.68
Pethidine	Paracetamol 325mg/Tramadol HCL 37.5mg	5	74.91±13.40	374.53
	Tramadol	20	822.48±653.4	16449.65
Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Paracetamol 325mg/Tramadol HCL 37.5mg	1	469.67±0.00	469.67
	Tramadol	6	160.38±74.98	962.29
Propoxyphene HCl 50mg/ Paracetamol 325mg/	Tramadol	3	191.71±115.38	575.14
Propoxyphene HCl 65mg/ Paracetamol 250mg/	Paracetamol 325mg/Tramadol HCL 37.5mg	1	342.94±0.00	342.94
	Tramadol	11	526.43±105.89	5790.71
Propoxyphene	Tramadol	1	27.22±0.00	27.22
Tilidine	Tramadol	1	298.13±0.00	298.13
Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	33	120.47±127.93	3975.00
Tramadol	Tramadol	90	134.18±123.61	12075.97

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Aspirin/Caffeine	Aspirin	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	1	92.35±0.00	92.35
Aspirin 500mg/Codeine 8mg	Aspirin	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	173.88±167.35	347.75
	Ibuprofen 200mg/Paracetamol 350mg	Orphenadrine 35mg/Paracetamol 450mg	1	75.06±0.00	75.06
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	138.52±15.09	415.53
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	114.57±0.00	114.57
	Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	112.95±0.00	112.95
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	259.68±0.00	258.68
		Pethidine	1	37.00±0.00	37.00
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	101.68±188.85	101.68
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	84.46±9.10	168.91
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Mefenamic acid	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	284.34±0.00	284.34
Aspirin	Ibuprofen 200mg/Paracetamol 250mg	Paracetamol	2	102.08±58.51	204.15
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	1	134.61±0.00	134.61
		Mefenamic acid	1	88.46±0.00	88.46
		Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 65mg	1	117.89±0.00	117.89
		Paracetamol	2	76.98±44.13	153.95

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Aspirin(continued)	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	92.51±0.00	185.02
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	116.59±0.00	116.59
		Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	162.22±0.00	162.22
	Ibuprofen	Paracetamol 500mg/ Mephenesin 150mg	1	123.01±0.00	123.01
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	99.79±0.00	99.79
		Paracetamol	3	110.21±45.47	330.62
	Paracetamol 100mg/ Aspirin 400mg/ Caffeine 30mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	62.45±7.40	124.89
		Paracetamol	3	44.19±20.47	132.59
	Paracetamol 500mg/ Codeine 10mg	Paracetamol	1	41.01±0.00	41.01
	Paracetamol 500mg/ Codeine 8mg	Paracetamol	1	70.73±0.00	70.73
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	51.86±0.00	51.86
		Paracetamol	1	3.37±0.00	3.37
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	173.33±0.00	173.33
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	2	98.9±17.89	197.80
		Tilidine	1	458.29±0.00	458.29
Buprenorphine	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Mefenamic acid	1	776.00±0.00	776.00

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Fentanyl	Morphine	1	1784.55±0.00	1784.55
	Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 400mg/Paracetamol 325mg	1	535.37±0.00	535.37
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	283.85±0.00	283.85
		Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	949.00±0.00	949.00
		Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	293.49±0.00	293.49
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	364.77±286.66	729.54
		Tramadol	3	813.01±165.98	2439.02
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	94.55±0.00	94.55
	Ketorolac Thomethane	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	119.88±0.00	239.76
	Morphine sulphate	Tilidine	1	317.57±0.00	317.57
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol	2	403.05±34.98	806.09
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Tramadol	1	190.64±0.00	190.64
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Tramadol	1	922.81±0.00	922.81
Fentanyl	Fentanyl	Paracetamol 325mg/Tramadol HCL 37.5mg	2	6335±0.00	12670.00
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Tramadol	1	1235.18±0.00	1235.18

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Fentanyl (continued)	Ketorolac Tromethane	Tramadol	1	963.37±0.00	936.37
	Propoxyphene	Tramadol	1	1729.85±0.00	1729.85
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol	1	167.25±0.00	167.25
	Ibuprofen	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	210.71±0.00	210.71
		Paracetamol	1	96.15±0.00	96.15
	Mefenamic acid	Mefenamic acid	2	161.78±33.80	323.56
		Orphenadrine 35mg/Paracetamol 450mg	1	197.86±0.00	197.86
		Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	123.39±19.33	246.77
		Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	92.68±0.00	92.68
		Paracetamol	6	132.30±63.87	793.79
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	197.99±0.00	197.99
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	96.61±14.14	386.44
		Paracetamol	2	122.31±7.69	244.62
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	71.24±0.00	71.24
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	40.42±0.00	40.42
		Paracetamol	1	86.13±0.00	86.13
Ibuprofen 400mg/Paracetamol 325mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	197.57±0.00	197.57
	Orphenadrine 35mg/Paracetamol 450mg	Tramadol	2	407.03±0.04	814.05

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Mefenamic acid	2	212.74±78.39	425.48
		Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	392.48±0.00	392.48
	Ibuprofen	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	380.42±0.00	760.84
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	236.80±0.00	236.80
		Paracetamol	1	323.67±0.00	323.67
	Mefenamic acid	Mefenamic acid	1	115.82±0.00	115.82
		Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	80.15±4.43	160.30
		Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	1	155.61±0.00	155.61
		Paracetamol	5	123.86±57.83	619.29
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	155.23±55.39	310.46
		Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	219.08±0.00	219.08
		Paracetamol 500mg/ Mephenesin 150mg	1	192.86±0.00	192.86
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	Paracetamol	1	127.64±0.00	127.64

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/ Paracetamol 250mg/ Codeine 10mg (continued)	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	3	182.95±0.00	548.86
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	150.96±0.00	301.92
		Paracetamol 500mg/ Mephenesin 150mg	1	165.93±0.00	165.93
		Paracetamol 325mg/Tramadol HCL 37.5mg	1	423.63±0.00	423.63
		Tramadol	1	436.32±0.00	436.32
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	103.66±0.00	103.66
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	129.00±87.87	386.99
		Propoxyphene HCl 65mg/ Paracetamol 250mg/	1	207.18±0.00	207.18
		Tramadol	3	220.13±75.83	660.38
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	97.19±0.00	97.19
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Tramadol	1	319.20±0.00	319.20
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	4	216.75±191.19	866.99
		Tramadol	1	237.49±0.00	237.49
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	85.88±0.00	85.88
	Paracetamol	Paracetamol	1	70.00±0.00	70.00
	Tramadol	Tramadol	2	300.37±210.97	600.74

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Mefenamic acid	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	198.41±163.62	369.81
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	214.401±0.00	214.40
		Paracetamol	1	148.70±0.00	148.70
	Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	59.18±0.00	59.18
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	296.13±0.00	296.13
		Aspirin 200mg/Paracetamol 200mg/ Chlorphenoxamine HCl 2mg/ Codeine phosphate 15mg/ Caffeine50mg/ Phenobarbitone 5mg	1	147.48±0.00	147.48
		Paracetamol	1	181.41±0.00	181.41
		Tramadol	2	123.38±110.45	246.76
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Tramadol	1	603.66±0.00	603.66
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	177.63±0.00	177.63
	Tramadol	Tramadol	3	141.81±0.00	425.44
Ibuprofen	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	3	74.57±23.81	223.72
		Paracetamol	2	53.93±27.03	107.85
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol	1	68.37±0.00	38.37
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	41.1±0.00	41.10

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	3	140.8±95.86	422.41
	Paracetamol	Paracetamol	2	85±9.37	169.99
Mefenamic acid	Mefenamic acid	Mefenamic acid	1	257.35±0.00	257.35
		Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	83.18±0.00	83.18
		Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	4	86.81±13.32	347.24
		Paracetamol	9	95.78±49.90	862.04
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	52.01±0.00	52.01
		Paracetamol	1	41.28±0.00	41.28
		Tramadol	8	220.97±31.75	1767.78
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 500mg/ Mephenesin 150mg	1	104.25±0.00	104.25
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	175.03±0.00	175.03
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	71.84±0.00	71.84
		Paracetamol	8	102.41±52.41	817.98
		Tramadol	1	216.64±0.00	216.64
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	41.99±0.00	41.99
		Paracetamol 325mg/Tramadol HCL 37.5mg	1	129.23±0.00	129.23
		Tramadol	1	114.53±0.00	114.53
	Paracetamol	Paracetamol	10	105.09±53.94	1050.89

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Morphine	Morphine	Paracetamol 325mg/Tramadol HCL 37.5mg	1	1281.26±0.00	1281.26
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	115.25±0.00	115.25
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	81.56±0.00	81.56
		Tramadol	2	523.85±378.73	1047.69
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	68.70±0.00	68.70
		Paracetamol 500mg/ Mephenesin 150mg	1	104.59±0.00	104.59
		Paracetamol	1	150.73±0.00	150.73
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	1	37.98±0.00	37.98
	Propoxyphene	Tramadol	2	426.90±0.00	853.80
	Tramadol	Tramadol	3	132.50±32.43	397.50
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 400mg/ Codeine phosphate 8mg/ Meprobamate 200mg	1	465.46±0.00	465.46
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	87.28±0.00	87.28
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Tramadol	1	513.11±0.00	513.11
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	40.68±0.00	40.68
		Paracetamol 325mg/Tramadol HCL 37.5mg	1	83.02±0.00	83.02
	Pethidine	Tramadol	2	238.94±187.97	477.87
	Tilidine	Paracetamol 325mg/Tramadol HCL 37.5mg	1	864.91±0.00	864.91

Table C 1 Utilisation of three analgesic medicine items in combination for the year 2004

Agents in combination			Number of Rx	Average cost	Total cost
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	96.66±0.00	96.66
Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	122.33±0.00	122.33
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	68.64±0.00	68.64
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	36.33±0.00	36.33
	Paracetamol	Paracetamol	2	59.55±0.00	119.10
		Tilidine	1	195.72±0.00	195.72
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol	Tramadol	3	1027.36±0.00	3082.09
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	116.49±10.68	166.49
Paracetamol 500mg/ Mephenesin 150mg	Tramadol	Tramadol	1	162.25±0.00	162.25
Paracetamol	Paracetamol	Paracetamol	2	47.8±0.00	95.60
		Tramadol	1	173.99±0.00	173.99
		Tilidine	1	236.74±0.00	236.74
Propoxyphene HCl 50mg/ Paracetamol 325mg/	Tramadol	Tramadol	1	181.10±0.00	181.10
Tilidine	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	864.32±0.00	864.32
Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	Tramadol	1	296.87±0.00	296.87

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Aspirin 500mg/Codeine 8mg	Aspirin	Paracetamol	1	153.51±0.00	153.51
	Ibuprofen 200mg/Paracetamol 250mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	8.47±0.00	8.47
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	235.68±0.00	235.68
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	137.74±0.00	137.74
		Paracetamol	1	10.40±0.00	10.40
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	52.38±0.00	52.38
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Ibuprofen 200mg/Paracetamol 250mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	66.72±0.00	133.44
Aspirin	Ibuprofen 200mg/Paracetamol 250mg	Paracetamol	2	113.19±64.79	226.38
	Ibuprofen 200mg/Paracetamol 350mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	88.88±60.83	177.75
		Paracetamol	1	63.52±0.00	63.52
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol	1	89.08±0.00	89.08
		Paracetamol 325mg/Tramadol HCL 37.5mg	1	79.27±0.00	79.27
		Tramadol	1	155.41±0.00	155.41
	Ibuprofen	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	63.82±0.00	127.64

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Aspirin (continued)	Ibuprofen (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	72.11±0.00	72.11
	Mefenamic acid	Paracetamol 500mg/Codeine phosphate 8mg	1	147.68±0.00	147.68
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	5	79.49±14.55	397.45
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	64.44±3.34	128.87
	Paracetamol 100mg/Aspirin 400mg/Caffeine 30 mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	46.64±31.75	93.28
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	34.48±0.00	34.48
		Paracetamol	3	38.23±11.82	114.68
	Aspirin	Paracetamol	1	41.27±0.00	41.27
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Dihydrocodeine tartrate	Dipanone HCl/Cyclizine	1	745.37±0.00	745.37
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	214.32±188.85	428.63
		Paracetamol 325mg/Tramadol HCL 37.5mg	2	430.34±0.00	860.68
	Mefenamic acid	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	45.64±0.00	45.64
	Orphenadrine 35mg/Paracetamol 450mg	Pethidine	2	162.81±32.04	325.61
	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Tramadol	1	288.76±0.00	288.76

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Tramadol	4	602.87±6.38	2411.48
	Tramadol	Tramadol	1	414.87±0.00	414.87
Dihydrocodeine tartrate	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	104.80±0.00	104.80
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	263.44±0.00	263.44
		Paracetamol	1	14.86±0.00	14.86
	Ibuprofen	Paracetamol	1	125.10±0.00	125.10
	Mefenamic acid	Paracetamol 500mg/ Mephenesin 150mg	1	40.11±0.00	40.11
		Paracetamol	2	158.5±47.39	317.18
	Morphine	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	689.48±0.00	68.48
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	111.63±38.96	558.18
	Paracetamol 500mg/ Codeine 8mg	Paracetamol 500mg/ Mephenesin 150mg	1	122.44±0.00	122.44
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	128.38±0.00	128.38
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	2	54.2±0.00	108.58
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	38.63±0.00	38.63
		Paracetamol	3	85.82±14.26	256.46

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	68.63±0.00	68.63
	Paracetamol	Paracetamol	2	127.39±12.66	254.78
	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Tramadol	1	211.15±0.00	211.15
Ibuprofen 200mg/Paracetamol 350mg	Ibuprofen 200mg/Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	111.33±0.00	111.33
	Mefenamic acid	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	51.35±0.00	51.35
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	86.43±0.00	86.43
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	66.81±0.00	66.81
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	3	69.00±18.55	206.99
Ibuprofen 400mg/Paracetamol 325mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 325mg/Tramadol HCL 37.5mg	2	150.05±0.00	300.10
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	299.35±0.00	299.35
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	2	331.79±21.15	663.57
	Ibuprofen	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	376.96±0.00	753.92

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Ibuprofen (continued)	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	212.41±0.00	212.41
		Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	56.06±0.00	56.06
	Mefenamic acid	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	91.47±44.15	274.40
		Paracetamol	2	77.99±51.83	155.98
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	131.32±0.00	262.64
		Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	22.23±0.00	221.23
		Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	2	228.87±0.00	457.74
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	111.35±0.84	222.69
		Paracetamol 500mg/ Mephenesin 150mg	1	102.11±0.00	102.11
		Tramadol	3	298.03±167.99	894.09
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	153.71±0.003	153.71
		Paracetamol	1	112.83±0.00	112.83
		Tramadol	2	327.02±109.45	654.04
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 500mg/ Mephenesin 150mg	1	275.69±0.00	275.69

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg (continued)	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	136.59±0.00	136.59
		Tramadol	1	72.14±0.00	726.14
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Tramadol	2	295.62±79.43	591.23
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	180.37±0.00	180.37
		Paracetamol	3	245.34±22.58	736.03
		Tramadol	1	83.83±0.00	83.83
	Paracetamol	Paracetamol	1	6.97±0.00	6.97
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Ibuprofen	Orphenadrine 35mg/Paracetamol 450mg	1	67.48±0.00	67.48
	Morphine	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	91.39±0.00	91.39
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	185.83±0.00	185.83
		Tramadol	1	127.25±0.00	127.25
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	2	134.26±33.06	268.52
		Tramadol	1	84.30±0.00	84.30
	Paracetamol	Tramadol	1	107.27±0.00	107.27
	Pethidine	Tramadol	1	144.82±0.00	144.82
Ibuprofen	Mefenamic acid	Paracetamol	2	46.11±10.65	92.22
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	1	87.75±0.00	87.75

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen (continued)	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	68.82±0.00	68.82
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	159.9±0.00	159.90
	Paracetamol	Paracetamol	2	92.61±0.00	185.22
Ibuprofen 200mg/Codeine phosphate 10mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 500mg/Codeine phosphate 10mg	1	65.88±0.00	65.88
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	134.28±0.00	134.28
Ketorolac tromethane	Tramadol	Tramadol	1	91.26±0.00	91.26
Mefenamic acid	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	75.02±0.00	75.02
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	116.73±0.00	116.73
		Paracetamol	1	76.13±0.00	73.13
	Orphenadrine 35mg/Paracetamol 450mg	Orphenadrine 35mg/Paracetamol 450mg	1	76.7±0.00	76.70
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	60.68±1.63	121.36
		Tramadol	2	222.19±18.22	444.38
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	56.91±0.00	56.91
		Paracetamol	7	78.31±38.93	548.20
	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	86.63±0.00	86.63

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Mefenamic acid (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	60.09±0.00	60.09
	Paracetamol	Paracetamol	2	94.22±16.82	188.43
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Tramadol	2	211.82±0.00	423.64
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	72.11±0.00	72.11
		Tramadol	1	96.00±0.00	96.00
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	56.96±0.00	56.96
		Paracetamol 500mg/ Mephenesin 150mg	1	139.19±0.00	139.19
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	96.68±0.00	193.36
		Paracetamol	3	59.86±4.72	179.58
	Paracetamol	Tramadol	2	150.82±135.81	301.63
	Tramadol	Tramadol	1	106.37±0.00	106.37
Paracetamol 500mg/Codeine phosphate 8mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	163.10±0.00	163.10
Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol	1	177.64±0.00	177.64
	Pethidine	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	2	145.30±0.00	290.60
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	66.84±0.00	66.84

Table C 2 Utilisation of three analgesic medicine items in combination for the year 2005

Agents in combination			Number of Rx	Average cost	Total cost
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg (continued)	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	83.70±0.00	83.70
		Paracetamol	1	25.47±0.00	25.47
	Pethidine	Tramadol	1	32.13±0.00	32.13
	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	94.46±0.00	94.46
Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	100.99±0.00	100.99
Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	118.98±81.01	237.96
		Paracetamol	2	45.25.±0.00	90.49
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	150.81±0.00	150.81
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	49.56±0.00	49.56
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	2	125.34±0.00	250.67
	Paracetamol	Paracetamol	3	64.25±10.68	192.74
	Tramadol	Tramadol	1	94.43±0.00	94.43
Paracetamol	Paracetamol	Paracetamol	1	35.03±0.00	35.03
	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	112.29±0.00	112.29
	Tramadol	Tramadol	1	545.41±0.00	545.41

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Aspirin 500mg/Codeine 8mg	Aspirin	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	165.48±0.00	165.48
Aspirin 200mg/ Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Orphenadrine 35mg/Paracetamol 450mg	1	215.49±0.00	215.49
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 325mg/Tramadol HCL 37.5mg	1	282.10±0.00	282.10
Aspirin	Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	97.4±0.00	97.40
		Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	29.23±0.00	29.23
		Paracetamol	1	121±0.00	121.00
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	223.36±0.00	223.36
		Paracetamol 200mg/ Codeine phosphate 10mg/ Caffeine 30mg/ Meprobamate 150mg	2	181.39±3.22	362.79
		Paracetamol	2	72.39±46.56	144.78
		Tramadol	2	295.66±20.18	591.32
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 400mg/ Codeine phosphate 8mg/ Phenyltoloxamine citrate 12mg/ Caffeine 32mg/	1	161.05±0.00	161.05
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	3	106.43±26.33	319.28
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	3	55.96±8.80	167.89
	Paracetamol	Paracetamol	3	79.08±41.33	237.23

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	1	215.98±0.00	215.98
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol	1	295.89±0.00	295.89
	Orphenadrine 35mg/Paracetamol 450mg	Tramadol	1	209.28±0.0	209.28
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Tramadol	1	427.11±0.00	427.11
		Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	796.93±0.00	796.93
	Pethidine	Tramadol	1	194.07±0.00	194.07
Fentanyl	Ibuprofen 200mg/Paracetamol 250mg	Paracetamol 325mg/Tramadol HCL 37.5mg	1	1199.68±0.00	1199.68
	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	1	695.21±0.00	695.21
	Orphenadrine 35mg/Paracetamol 450mg	Tramadol	1	1165.02±0.00	1165.02
Ibuprofen 200mg/Paracetamol 250mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	135.30±0.00	135.30
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	102.95±0.00	102.95
	Mefenamic acid	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	111.82±0.00	111.82
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	5	64.51±29.52	322.53
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	88.88±0.00	88.88
		Paracetamol	1	26.36±0.00	26.36
	Paracetamol	Tramadol	1	47.99±0.00	47.99

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg	Mefenamic acid	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	65.92±0.00	65.92
		Paracetamol 500mg/ Mephenesin 150mg	1	47.62±0.00	47.62
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	80.04±0.00	80.04
	Paracetamol 500mg/Codeine phosphate 20mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	193.64±0.00	193.64
Ibuprofen 400mg/Paracetamol 325mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Tramadol	1	654.44±0.00	654.44
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	1	193.50±0.00	193.50
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	137.50±39.30	274.99
		Paracetamol	1	202.46±0.00	202.46
		Propoxyphene HCl 50mg/ Paracetamol 325mg/	1	126.77±0.00	126.77
	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	110.09±0.00	110.09
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	10	109.27±0.00	1092.70
	Ibuprofen	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	227.24±0.27	454.48
		Paracetamol 500mg/ Mephenesin 150mg	1	124.51±0.00	124.51

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/ Paracetamol 250mg/ Codeine 10mg	Mefenamic acid	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	74.69±0.00	74.69
		Paracetamol	1	182.95±0.00	182.95
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	87.99±6.09	175.97
	Paracetamol 500mg/ Codeine 10mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	166.62±0.00	166.62
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	59.49±0.00	59.49
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	4	91.77±10.24	367.08
		Paracetamol	1	47.13±0.00	47.13
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 500mg/ Mephenesin 150mg		127.90±0.00	127.90
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	70.23±0.00	70.23
		Paracetamol	1	155.72±0.00	115.72
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	1	83.09±0.00	83.09
		Paracetamol	1	72.00±0.00	72.00
		Tramadol	1	131.33±0.00	131.33
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	68.93±0.00	68.93
	Paracetamol	Paracetamol	1	61.86±0.00	61.86
	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	76.88±0.00	76.88
	Tramadol	Tramadol	1	111.23±0.00	111.23

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Mefenamic acid	Tramadol	1	148.27±0.00	148.27
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	108.24±0.00	108.24
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	104.29±0.003	104.29
		Tramadol	1	169.36±0.00	169.36
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	1	212.90±0.00	212.90
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	89.14±0.00	89.14
		Paracetamol	1	140.84±0.00	140.84
		Pethidine	1	84.67±0.00	84.67
	Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Tramadol	1	298.34±0.00	298.34
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	81.17±0.00	81.17
	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	158.30±0.00	158.30
Ibuprofen	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	82.35±0.00	82.35
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	91.2±0.00	91.20
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	89.87±0.00	89.87

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Codeine phosphate 10mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	72.22±0.00	72.22
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	1	54.97±0.00	54.97
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	125.51±0.00	125.51
Mefenamic acid	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	82.32±16.17	164.63
		Paracetamol	1	48.54±0.00	48.54
		Tramadol	1	85.38±0.00	85.38
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	5	70.42±37.79	352.09
	Paracetamol	Paracetamol	3	71.17±29.38	213.52
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 500mg/Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	44.22±0.00	44.22
	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	1	84.18±0.00	84.18
		Tramadol	1	663.13±0.00	663.13
	Paracetamol 400mg/ Codeine phosphate 8mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	61.366±0.00	61.36
	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	2	64.45±16.43	128.89
		Paracetamol 500mg/ Mephenesin 150mg	1	51.59±0.00	51.59
		Paracetamol	1	55.89±0.00	55.89

Table C 3 Utilisation of three analgesic medicine items in combination for the year 2006

Agents in combination			Number of Rx	Average cost	Total cost
Orphenadrine 35mg/ Paracetamol 450mg (continued)	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	113.79±0.00	113.79
		Paracetamol 500mg/ Mephenesin 150mg	2	80.89±17.52	161.96
		Paracetamol	1	133.82±0.00	133.82
		Tramadol	1	174.78±0.00	174.78
	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	57.71±0.00	57.71
	Paracetamol	Tramadol	1	61.29±0.00	61.29
	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	1	146.91±0.00	146.91
	Propoxyphene HCl 50mg/ Paracetamol 325mg/	Tramadol	1	372.36±0.00	372.36
	Paracetamol 325mg/Tramadol HCL 37.5mg	Tramadol	1	45.93±0.00	45.93
	Tramadol	Tramadol	2	106.39±0.00	212.77
Paracetamol 500mg/Codeine phosphate 20mg	Paracetamol 120mg/ Codeine phosphate 5mg/ Prometasien HCl 6.5mg	Paracetamol	1	131.86±0.00	131.86
Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Pethidine	1	99.34±0.00	99.34
	Tramadol	Tramadol	1	1072.88±0.00	1072.88
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	38.72±0.00	38.72
	Paracetamol	Paracetamol	1	158.38±0.00	158.38
	Pethidine	Tramadol	1	74.17±0.00	74.17
	Tramadol	Tramadol	2	1098.69±3.18	2197.38
Paracetamol	Tramadol	Tramadol	1	78.97±0.00	78.97

Table D1 Utilisation of four analgesic medicine items in combination for the year 2004

Agents in combination				Number of Rx	Average cost	Total cost
Aspirin 500mg/Codeine 8mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	128.67± 0.00	128.67
Aspirin	Mefenamic acid	Mefenamic acid	paracetamol	1	13.47± 0.00	13.47
	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	Paracetamol	1	128.38± 0.00	128.38
Fentanyl	Fentanyl	Fentanyl	Fentanyl	4	9082.11± 0.00	9082.11
Ibuprofen 200mg/Paracetamol 250mg	Mefenamic acid	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	219.48± 0.00	219.48
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol	1	162.28± 0.00	162.28
	Mefenamic acid	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol	1	210.07± 0.00	210.07
	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	125.58± 0.00	125.58
Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	232.79± 0.00	232.79

Table D 2 Utilisation of four analgesic medicine items in combination for the year 2005

Agents in combination				Number of Rx	Average cost	Total cost
Aspirin	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	Paracetamol	1	81.01± 0.00	81.01
Ibuprofen 200mg/Paracetamol 250mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol	Tramadol	1	231.85± 0.00	231.85
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Morphine sulphate	Tramadol	Tramadol	1	128.28± 0.00	128.28
Orphenadrine 35mg/Paracetamol 450mg	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	73.75± 0.00	73.75
Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	Paracetamol	1	73.23± 0.00	73.23
Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	1	918.06± 0.00	918.06

Table D 3 Utilisation of analgesic medicine items in combination for the year 2006

Agents in combination				Number of Rx	Average cost	Total cost
Aspirin 500mg/Codeine 8mg	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	107.05± 0.00	107.05
Aspirin	Parcetamol 120mg/Codeine phosphate 5mg/Prometazine HCl 6.5mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	95.38± 0.00	95.38
Dextropropoxyphene HCl 65mg/ Paracetamol 400mg/ L-glutamine 25mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	1	1267.66± 0.00	1267.66
Dipipanone HCl/Cyclizine	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Ketorolac thomethane	Propoxyphene	1	510.66± 0.00	510.66
Ibuprofen 200mg/Paracetamol 250mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 500mg/ Mephenesin 150mg	Paracetamol	1	58.98± 0.00	58.98
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 350mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	231.75± 0.00	231.75
			Paracetamol 500mg/ Mephenesin 150mg	3	164.84± 32.84	202.14
		Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol	1	305.82± 0.00	305.82

Table E 1 Utilisation of five analgesic medicine items in combination for the year 2005

Agents in combination					Number of Rx	Average cost	Total cost
Paracetamol 500mg/ Dextropopoxyphene 50mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 65mg/ Aspirin 375mg/ Caffeine 30mg	Tramadol	1	1239± 0.00	1239.42

Table E 2 Utilisation of five analgesic medicine items in combination for the year 2006

Agents in combination					Number of Rx	Average cost	Total cost
Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Ibuprofen 200mg/Paracetamol 250mg/ Codeine 10mg	Orphenadrine 35mg/Paracetamol 450mg	Paracetamol 320mg/ Codeine phosphate 8mg/ Caffeine 32mg/ Meprobamate 150mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	1	147.24± 0.00	147.24
Paracetamol 400mg/ Codeine phosphate 10mg/ Diphenhydramine HCl 5mg/ Caffeine 50mg/ Phenobarbitone 8mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Paracetamol 450mg/ Doxylamine succinate 5mg/ Caffeine 450mg/ Codeine phosphate 10mg	Propoxyphene HCl 65mg/ Paracetamol 250mg/	Tramadol	1	51.69± 0.00	51.69

Prescribing Patterns of Combination Analgesic Drugs in a Section of the Private Health Care Sector in South Africa

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Purpose:
The general objective of this study was to investigate the prescribing patterns (usage and cost) of combination analgesic drugs, in a section of the private health care sector in South Africa by using a medicine claims database.

Methods:
A quantitative, retrospective drug utilisation review was performed on data from a medicine claims database for the years 2001, 2002, 2004, 2005 and 2006.

Results:
Combination analgesic drugs represented 8.87% (n=261 907) of all medicine claimed during 2001 (N=2 951 326), decreased to 7.20% (n=381 809) during 2004 (N=5 305 846) after which it increased to 7.92% (n=187 745) in 2006 (N=2 370 572). Between 2001 (N=R379 708 489.00) and 2006 (N=R279 160 832.00) the cost percentage of the combination analgesic drugs decreased from 4.95% (n=R18 798 202.42) to 3.15% (n=R8 791 228.57).

The average cost per combination analgesic drugs decreased from R71.77 ± 61.67 to R46.83 ± 43.41 between 2001 and 2006. This decrease was not of practical significance (d<0.8). The average number of combination analgesics per prescription stayed relatively constant from 2001 to 2006.

The percentage generic combination analgesic drugs claimed increased from 29.63% (n=77 608) in 2001 to 66.37% (n=124 600) in 2006 (N=261 907 for 2001 and N=187 745 for 2006) even though generic medicine items claimed by the total database only increased from 26.79% (n=790 548) in 2001 to 40.27% (n=954 561) during 2006 (N=2 951 326 for 2001 and N=2 370 572 for 2006).

The combination of ibuprofen 200mg, paracetamol 250mg and codeine phosphate 10mg represents the active ingredient combination with the highest prevalence for the entire study period, increasing from 28.44% (n=74 483) in 2001 to 33.08% (n=62 100) in 2006 of all combination analgesics prescribed (N=261 907 for 2001 and N=187 745 for 2006).

Conclusion:
The prevalence of combination analgesics decreased from 2001 to 2004 and increased between 2004 and 2006. The cost of combination analgesic drug therapy decreased from 2001 to 2006. The change in prevalence could be due to an increased availability of combination analgesic medicine, or a decrease in the cost of therapy. The decrease in the cost of drug therapy is probably a result of the implementation of the Generic Substitution Guidelines in April 2003 and the implementation of the new pricing regulations during May 2004.