PRESCRIBING PATTERNS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS FOR THE PERIOD 2001 UNTIL 2006

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A Short History of Medicine

2000 B.C. – "Here, eat this root."

1000 B.C. – "That root is heathen, say this prayer."

1850 A.D. – "That prayer is superstition , drink this potion."

1940 A.D. – "That potion is snake oil, swallow this pill."

1985 A.D. – "That pill is ineffective, take this antibiotic."

2000 A.D. – "That antibiotic is artificial. Here, eat this root."

~Anon~

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Abstract

Title: Prescribing patterns of angiotensin-converting enzyme inhibitors for the period 2001 until 2006.

Keywords: ACE inhibitors, hypertension, congestive heart failure, cardiovascular diseases, pharmacoeconomics, drug utilisation review, cost savings, innovator, generic, prevalence, active ingredient, pricing regulations

ACE inhibitors alone normalize blood pressure in approximately 50% of patients with mild- to- moderate hypertension, and many consider ACE inhibitors as first-line drugs for the treatment of high blood pressure (Jackson & Garrison, 1996:747). In addition to this ACE inhibitors have been demonstrated to be cost-effective in congestive heart failure and their cost is decreasing. There may be therefore a true need to encourage increasing use of ACE inhibitors in patients with chronic heart failure, particularly in general practice, to provide cost-effective optimal treatment in health care systems with limited financial resources (Szucs, 1997:278S).

The objectives of this study were to investigate the prescribing patterns and cost of angiotensin-converting enzyme (ACE) inhibitors. The method included a longitudinal retrospective drug utilisation study, done on ACE inhibitors claimed through a national medicine claims database in a sector of the private healthcare system in South Africa. The periods were divided into 2001-2002, 2004, 2005 and 2006. The periods of 2004, 2005 and 2006 were then subdivided into four monthly periods, but not 2001-2002, because it was only used as an instrument for comparison purposes, as there were no changes in pricing regulations.

The results showed that the contribution made by ACE inhibitor containing prescriptions to the total number of prescriptions showed a continuous decrease of 0.57% (n=77853) from 2004 until 2005 and then a decrease by 0.89% (n=49450) from 2005 until 2006. The total number of ACE inhibitor items claimed through the database showed a decrease of 0.54% (n=78447) from 2004 until 2005 and then a larger decrease of 0.57% (n=49661) from 2005 until 2006.

The prevalence of ACE inhibitor innovators as part of all innovators decreased by 0.66% (n=53292) from 2004 until 2005 and decreased further by 0.25% (n=26678) from 2005 until 2006. The contribution made by the ACE inhibitor generics as

percentage of all generics showed a decrease of 0.38% (n=25155) from 2004 until 2005 and a further decrease of 1.18% (n=22983) from 2005 until 2006. The decrease might be attributed to the reduction in the number of medical schemes from 2004 until 2006.

On 2 August 2004 the "full" implementation of the pricing regulations was experienced and thus showed the lowest average cost per item for ACE inhibitors of R134.60 ± R73.83. The average cost per ACE inhibitor item decreased with 12.86% (R24.02) from Jan 2004-Apr 2004 (phase before the pre-implementation phase of the pricing regulations) until May 2004-August 2004 (pre implementation phase of the pricing regulations). After that the average cost per ACE inhibitor item decreased by 27.92% (R52.14) from May 2004-Aug 2004 until Sept 2004-Dec 2004. Even *though the average cost per ACE inhibitor item increased and decreased during* 2004 to 2006, the overall average cost decreased by 5.43%. The reduction might be due to the increased utilisation of generics as well as the influence of the single exit price.

Cardiovascular, antihypertensive and ACE inhibitor items showed that the total cost as percentage of all medicine items decreased from 2004 until 2006 by 4.36%, 2.12% and 0.98% respectively. This might be due to the reduction in the number of prescriptions from the database.

ACE inhibitor innovator and generic items showed a reduction in expected cost saving percentage with the SEP from Sept 2004-Dec 2004 until Sept 2005-Dec 2005 of 0.49% and 0.65% respectively. The expected cost savings of total ACE inhibitor items decreased with 0.42%.

The active ingredient with the highest prevalence percentage during 2001-2002 was enalapril (15.21%) followed by perindopril (15.10%). From 2004 until 2006 the items with the largest prevalence percentage were perindopril and indapamide/perindopril. Both of these active ingredients showed a continuous increase in prevalence percentage from 2004 to 2006. It is also recommended to determine ACE inhibitor use and cost in specific diseases, as well as combination therapy with other antihypertensive medicines.

Opsomming

Titel: Voorskryfpatrone van angiotensien-omskakelings ensiem inhibeerders vir die tydperk 2001 tot 2006.

Sleutelwoorde: AOE inhibeerders, hipertensie, kongestiewe hartversaking, kardiovaskulêre siektes, farmako-ekonomie, medisyneverbruiksevaluering, koste besparings, innoveerder, generies, voorkoms, aktiewe bestanddeel, prys regulasies, enkele-uitgangs prys (EUP)

AOE inhibeerders normaliseer bloeddruk in ongeveer 50% van pasiënte met ligte tot matige hipertensie en AOE inhibeerders word deur baie oorweeg as eerste-linie medisyne vir die behandeling van hoë bloeddruk (Jackson & Garrison, 1996:747). Verder het AOE inhibeerders bewys dat dit koste-effektief is in kongestiewe-hartversaking en hulle koste is besig om te daal. Daar is dus 'n toenemende behoefte aan die verbruik van AOE inhibeerders in pasiënte met kroniese hartversaking, veral in die algemene praktyk om koste-effektiewe optimale behandeling te voorsien in gesondheidsorg sisteme met beperkende finansiële hulpbronne (Szucs, 1997:278S).

Die doel van hierdie studie was om die voorskryfpatrone en koste van AOE inhibeerders te bepaal. 'n Longitudinale retrospektiewe medisyneverbruiks evaluering is gedoen op AOE inhibeerders, geëis deur 'n nasionale medisyne-eis databasis in 'n sektor van die private gesondheidsorg sisteem in Suid-Afrika. Die periodes is verdeel in 2001-2002, 2004, 2005 en 2006. Die periodes van 2004, 2005 en 2006 is verder verdeel in vier-maandelikse periodes, behalwe 2001-2002, omdat dit slegs gebruik is as maatstaf vir vergelykende doeleindes, aangesien daar geen veranderinge in prys regulasies gedurende hierdie tydperk was nie.

Die resultate het gewys dat die bydrae wat die AOE inhibeerder bevattende voorskrifte tot die totale aantal voorskrifte gemaak het, afgeneem het met 0.57% (n=77853) van 2004 tot 2005 en het verder afgeneem met 0.89% (n=49450) van 2005 tot 2006. Die totale aantal AOE inhibeerder items geëis deur die databasis het afgeneem met 0.54% (n=78447) van 2004 tot 2005 en 'n groter afname van 0.57% (n=49661) vanaf 2005 tot 2006.

Die voorkoms van AOE inhibeerder innoveerders, as deel van alle innoveerders, het afgeneem met 0.66% (n=53292) vanaf 2004 tot 2005 en daarna 'n verdere afname van 0.25% (n=26678) vanaf 2005 tot 2006. Die bydrae wat deur generiese AOE

inhibeerders gemaak is as 'n persentasie van alle generies items het 'n afname van 0.38% (n=25155) getoon vanaf 2004 tot 2005 en daarna 'n verdere afname van 1.18% (n=22983) vanaf 2005 tot 2006. Hierdie afname kan moontlik toegeskryf word aan die afname van die aantal medies skemas vanaf 2004 tot 2006.

Op 2 Augustus 2004 was die "volle" implementering van die prys regulasies in werking en het gelei tot die laagste gemiddelde koste per item vir AOE inhibeerders van R134.60 ± R73.83. Die gemiddelde koste per AOE inhibeerder item het afgeneem met 12.86% (R24.02) vanaf Jan 2004-Apr 2004 (fase voor die pre-implementerings fase van die prys regulasies) tot Mei 2004-Aug 2004 (pre-implementerings fase van die prys regulasies). Hierna het die gemiddelde koste per AOE inhibeerder item afgeneem met 27.92% (R52.14) vanaf Mei 2004-Aug 2004 tot Sep 2004-Des 2004. Alhoewel die gemiddelde koste per AOE inhibeerder item toegeneem en afgeneem het gedurende 2004 tot 2006, het die algehele gemiddelde koste afgeneem met 5.43%. Die afname kan moontlik toegeskryf word aan die toename in die verbruik van generiese items, asook die invloed van die enkel-uitgangsprys.

Die totale koste van kardiovaskulêre, antihipertensiewe en AOE inhibeerder items het 'n onderskeidelike afname getoon van 4.36%, 2.12% en 0.98% vanaf 2004 tot 2006 as persentasie van alle medisyne items. Hierdie afnames kan moontlik toegeskryf word aan die afname in die aantal voorskrifte geëis vanaf die databasis.

AOE inhibeerder innoveerder en generiese items het 'n afname in die beoogde koste besparings persentasie met die EUP vanaf Sep 2004-Des 2004 tot Sep 2005 tot Des 2005 met onderskeidelik 0.49% en 0.65%. Die beoogde koste besparings van die totale AOE inhibeerder items het afgeneem met 0.42%.

Die aktiewe bestanddeel met die grootste voorkoms persentasie gedurende 2001-2002 was enalapril (15.21%) gevolg deur perindopril (15.10%). Vanaf 2004 tot 2006 was perindopril en indapamied/perindopril die items met die grootste voorkoms persentasie. Beide hierdie aktiewe bestanddele het getoon op 'n konstante toename in voorkoms persentasie vanaf 2004 tot 2006. Daar word ook voorgestel dat die AOE inhibeerder verbruik asook koste in spesifieke siektes bepaal word, sowel as kombinasie terapie met ander antihipertensiewe medisyne.

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Chapter 1

Introduction

1.1 Introduction

The focus of this study is to investigate the prescribing patterns and cost of angiotensin-converting enzyme (ACE) inhibitors in a section of the private health care sector for the period 2001 until 2006 by using a medicine claims database.

1.2 Problem statement

Despite the fact that ACE inhibitors have been shown to improve symptoms, reduce the incidence of clinical events associated with disease worsening, and reduce hospitalizations, ACE inhibitors remain underused (Szucs, 1997:277S).

Hypertension is a global health burden affecting developed and developing countries, and South Africa is no exception. The high prevalence of hypertension worldwide has contributed to the present and expected pandemic of cardiovascular disease (CVD) and this is of particular concern in developing countries (Seedat *et al.*, 2006:338). Hypertension is a costly and major contributor to CVD. In 1991, CVD accounted for R4 to R5 billion in direct and indirect costs. This expenditure constituted 7.5% of the direct health care spending in South Africa (Seedat *et al.*, 2006:338). Cardiovascular disease has shown to be the highest cause of mortality in South Africa, with 4 of the top 20 causes of death accounting for 7.4% of all deaths (Seedat *et al.*, 2006:337).

Szucs (1997:277S) reported that the cost effectiveness of captopril therapy compares favourably with many other cardiac interventions; for example, US$3200 to US$18,400/ life year saved with β-blockers after myocardial infarction (MI) and US$ 21,200 to US$ 22,400/ life year saved using streptokinase in suspected acute myocardial infarction (MI) in elderly patients. Thus, ACE inhibitor therapy not only reduces mortality and the incidence of heart failure, but is also cost-effective in patients with asymptomatic left ventricular dysfunction following an acute myocardial infarction.

The Heart Outcomes Prevention Evaluation Study (HOPE) convincingly showed the benefit of ACE inhibitor therapy in the prevention of cardiovascular events as compared with a placebo (Nordmann *et al.*, 2003:581). The use of ACE inhibitors in Italy between 1988 and 1998 increased from 13.4 to 46.7% prior to hospitalisation, and from 25.8% to 59.2% as a discharge prescription (Antonelli *et al.*, 2002:516).

According to the Prescription Pricing Authority in England (2004) prescribing of renin-angiotensin system drugs has more than doubled in the last 5 years with cost increasing by 91 % (7.6 million items, £122 million). ACE inhibitor prescribing has grown to 5.8 million items, costing £76.2 million per quarter. The most commonly prescribed ACE inhibitors in England during 2004 were ramipril and lisinopril (2.0 million and 1.7 million items, costing £31.2 million and £8.2 million respectively, per quarter).

In addition, ACE inhibitors have been demonstrated to be cost-effective in congestive heart failure and their cost is declining. There may be therefore a true need to encourage increasing use of ACE inhibitors in patients with chronic heart failure, particularly in general practice, to provide cost-effective optimal treatment in health care systems with limited financial resources (Szucs, 1997:278S).

Antonelli *et al.* (2002:516-521) found that the use of ACE- inhibitors for the treatment of chronic heart failure has progressively increased both at home and in general medicine and geriatric hospital wards in a 10-year study period. They found that digitalis and diuretics continue to be the most commonly prescribed drugs. A widespread educational effort is needed to increase physicians' awareness of the rationale for prescribing ACE-inhibitors for chronic heart failure patients.

Seletswane (2004:145) found that in the South African private health care sector the majority of ACE inhibitors prescribed during the twelve-month study period were for the innovator products, with a prevalence of 82.56%. The use of the generic ACE inhibitors, with a prevalence of 17.44% (n=68 162). Seletswane (2004:145) further found that if only the prescriptions containing ACE inhibitor items that have generic equivalents were to be substituted with their generic equivalents, R899 751.29 (6.5%) would be saved. Therefore, the use of ACE inhibitor generic equivalent drugs can result in a dramatic reduction in the costs of ACE inhibitor therapy in the South African health care sector.

The purpose of this study is to determine if similar results were achieved in the South African private health care sector for the period 2001-2006. The study will evaluate aspects of cost and prescription patterns of the ACE inhibitors. The study will also determine the effects that the change in pricing regulations had on prescribing patterns and cost of ACE inhibitors.

1.3 Research questions

The following research questions will be answered in this study.

- What do drug utilization and managed care entail?
- What do pharmacoeconomics entail?
- What do the "new" pricing regulations entail?
- What does the management and of hypertension and congestive heart failure entail?
- What is the prevalence of prescribing ACE inhibitors according to literature and the database?
- How does generic substitution influence prescription patterns and cost of innovator drugs, according to the database?
- What is the effect of the new pricing regulations (implemented in 2004) on the prescribing patterns and cost of ACE inhibitors?
- How do the ACE inhibitors in the top 50 items, according to total cost, from Interpharm® Datasystems compare to the top 50 items from Mediscor®.
- Determine the use of generic substitution with regard to ACE inhibitors.

1.4 Research objectives

1.4.1 General research objectives

The general objective of the study is to investigate the prescribing patterns, cost and the possible effect of generic substitution on the prescribing patterns of ACE inhibitors for the period 2001 until 2006 by using a medicine claims database.

1.4.2 Specific objectives

The specific objectives from the literature study are to:

- Discuss the management of hypertension, congestive heart failure and other cardiovascular diseases, with emphases on ACE inhibitors in these diseases according to literature.
- Determine the prevalence of hypertension and congestive heart failure according to literature.
- Indicate what the "new" pricing regulations (implemented in 2004) entail.

- Indicate according to the literature the relevance of using combination therapy in conjunction with ACE inhibitors for cardiovascular diseases.
- Indicate what the basic aspects of pharmacoeconomics entail.
- Indicate the fundamentals of drug utilisation review and managed care.
- Determine the use of generic substitution with regard to ACE inhibitors.

The specific research objectives of the empirical investigation are to:

- Determine the overall cost and prescribing patterns of all medicine items on the total database including cardiovascular, antihypertensive and ACE inhibitor items.
- Determine the cost and overall prescribing patterns of innovator and generic products from the total database with reference to cardiovascular, antihypertensive and ACE inhibitor items.
- Determine the potential savings of all medicine item costs with regard to the single exit price (SEP) (refer to chapter 3, section 3.4.2.5).
- Investigate the prevalence of ACE inhibitor active ingredients
- Investigate the prevalence percentage by which ACE inhibitors form part of all the antihypertensive as well as cardiovascular items.
- Investigate the cost analyses of the top 20 ACE inhibitors according to prevalence
- Determine the prevalence and cost of the individual ACE inhibitor items
- Indicate which new ACE inhibitors came on the market during the appropriate study periods.
- Investigate the combination of ACE inhibitors and other antihypertensive products on the same prescription
- Reveal the number of prescriptions per patient containing at least one ACE inhibitor
- Determine the prescribed daily dose (PDD) and effect sizes between ACE inhibitor active ingredient innovators and generics.
- Determine the ACE inhibitors on the list of top 50 products of Interpharm® Datasystems and comparing it to the ACE inhibitors on the list of top 50 products Mediscor®, according to prevalence and cost.

1.5 Research Methodology

The study consists of two phases, namely a literature review and an empirical investigation.

1.5.1 Phase 1: Literature review

The first part of the literature review focuses on the indications of ACE inhibitors, pharmacological and non-pharmacological aspects with the treatment of cardiac diseases relating to ACE inhibitor treatment.

The second part of the literature review focuses on pharmacoeconomics and drug utilization in regard to prescribing patterns, cost and generic substitution of ACE inhibitors in cardiovascular disorders.

1.5.2 Phase 2: Empirical investigation

The empirical investigation entails the following:

- Selecting appropriate data

A quantitative, retrospective drug utilization study done on data provided by a medicine claims database, Interpharm® Datasystems for the period of 2001 to 2006.

- Selecting the appropriate measuring instruments

Measuring instruments used in this study include prevalence and cost (refer to chapter 4, section 4.9).

- Using appropriate statistical methods

Statistical methods used in this study include arithmetic mean (average), effect size (d-value) and cost-prevalence index (CPI) (refer to chapter 4, section 4.8.2.2, 4.8.2.3, 4.8.2.4 and 4.8.2.5).

- Data analysis

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

The data are analyzed and compared, using Statistical Analysis System (SAS® for Windows, 9.1, 2006). A comparison is done on data from January 2001 to December 2006 in three study periods, namely January to April, May to August and September to December. Furthermore, data from 2003 were not available in electronic format and are thus not included in this study. The aspects of age and gender were also not available in electronic format and are thus not included in this study.

- Ethical aspects

Approval was obtained for the study from the Pharmacy Benefit Management (PBM) as well as from the research committee of the North-West University to conduct this drug utilization study. Data used in the analyses were obtained where 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. Therefore, no specific patient, medical practice, pharmacy or medical scheme could be identified and confidentiality of information was maintained throughout the study

- Results and discussion of results

Results from the data are illustrated by using appropriate graphs and/or tables, discussed and compared over different time periods in chapter 5.

- Conclusion, limitations and recommendations of the empirical study

The data and results from chapter 5 are concluded in chapter 6. Limitations and recommendations from the study are identified and summarized in chapter 6.

1.6 Chapter division

Chapter 1: Introduction

Chapter 2: The nature of ACE inhibitors, cardiovascular medicine and relevant diseases

Chapter 3: An overview of pharmacoeconomics, drug utilization review and managed care

Chapter 4: Objectives and methodology

Chapter 5: Results and discussion

Chapter 6: Conclusions, recommendations and limitations

1.7 Chapter summary

In this chapter an overview of the problem statement was presented and research questions were stated. This chapter further contained general and specific research objectives as well as the research methodology and chapter division.

Chapter 2 contains an overview of hypertension, congestive heart failure as well as an overview and the use of ACE inhibitors in these diseases. Chapter 2 further contains aspects of combination therapy with ACE inhibitors and concludes with an overview of generic substitution.

Chapter 2

The nature of ACE inhibitors, cardiovascular medicines and relevant diseases

In this chapter, although not directly part of the study, it is important to take note of the nature and extent of not only the cardiovascular diseases (in a broad sense), but also to of the occurrence and extent of cardiovascular diseases. In this chapter the mechanisms of cardiovascular medicine; pharmacokinetics, side-effects, and contra-indications will be identified and briefly discussed. The chapter will conclude with the aspects of generic substitution.

2.1 The Renin-angiotensin-aldosterone system

Angiotensin-converting enzyme (ACE) inhibitors are now established drug therapies in two of the most common cardiologic conditions, such as hypertension and congestive heart failure (Opie, 1992: preface).

In hypertension, these agents are rapidly increasing their share of the market, and in congestive heart failure, they have proven benefits on mortality besides being relatively simple to use (Opie, 1992: preface). Although they are considerably more expensive than diuretics for hypertension or digoxin for congestive heart failure, they seem to be progressively displacing these less expensive agents (Opie, 1992: preface).

Bundkirchen and Schwinger (2004:D59) stated that in the *"treatment trial"* (patients with left ventricular dysfunction and overt heart failure) the probability that enalapril improved survival and decreased costs was 0.94. In the "*prevention trial*" (patients with left ventricular dysfunction without overt heart failure) the cost per life year saved was estimated to be $1820. This study indicated that ACE inhibitors are highly cost-effective and provide benefits in heart failure patients.

2.1.1. A short overview of the mechanism of raising blood pressure

The renin-angiotensin system may be the most important of the endocrine systems that affect the control of blood pressure. Renin is secreted from the juxtaglomerular apparatus of the kidney in response to glomerular under perfusion or a reduced salt intake. It is also released in response to stimulation from the sympathetic nervous system. Renin is responsible for converting rennin substrate (angiotensinogen) to angiotensin-I, a physiologically inactive substance which is rapidly converted to angiotensin-II in the lungs by angiotensin converting enzyme (ACE). Angiotensin-II is a potent vasoconstrictor and thus causes a rise in blood pressure. In addition it stimulates the release of aldosterone from the zona glomerulosa of the adrenal gland, which results in a further rise in blood pressure related to sodium and water retention (see figure 2.1) (Beevers *et al.*, 2001:913).

Beevers *et al.* (2001:913) also mentioned that there is, however, increasing evidence that there are important non-circulating "local" renin-angiotensin epicrine or paracrine systems, which also control blood pressure. Local renin systems have been reported in the kidney, the heart, and the arterial tree. They may have important roles in regulating regional blood pressure.

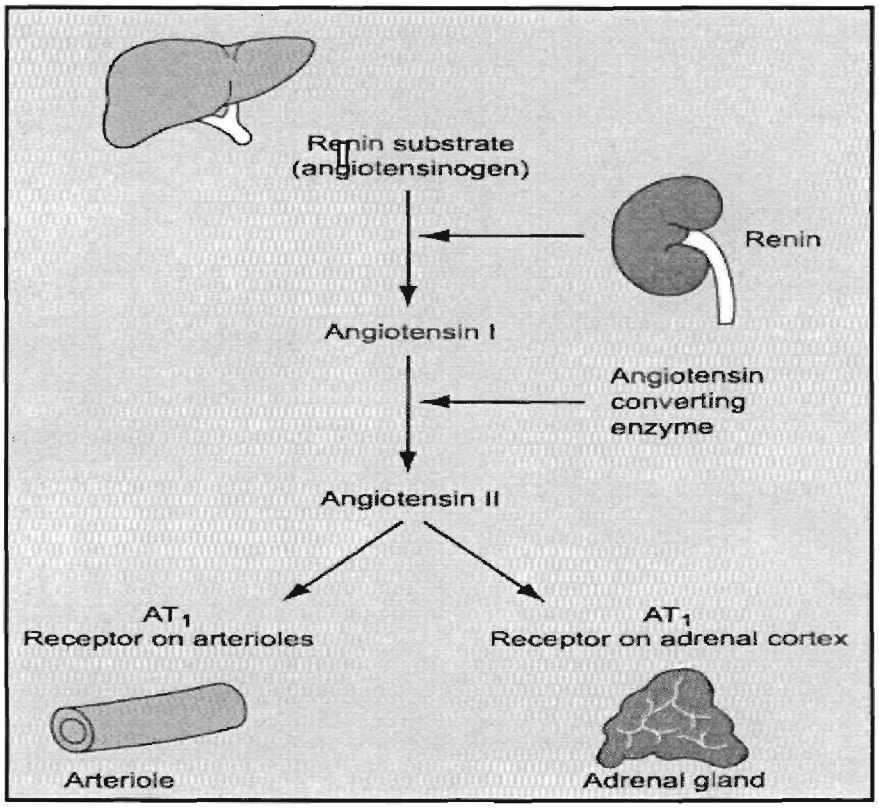


Figure 2.1: Renin-angiotensin system and effects on blood pressure and aldosterone release (Beevers *et al.*, 2001: 913).

2.1.2 The angiotensin-converting enzyme

This angiotensin-converting enzyme is a ubiquitous enzyme found in endothelial cells throughout the body and in epithelial cells in the kidney, gastrointestinal tract, choroids plexus and placenta. It has also been shown to be present in germinal cells and spermatozoa in the testis. It has an extensive but discrete localization in the central nervous system where it has been shown to be both in neuronal and in dendritic cells (Johnston, 1989:1100). Angiotensin-I converting enzyme, or kinase-II, is a dipeptidyl carboxypeptidase that plays an important role in blood pressure regulation and electrolyte balance by hydrolyzing angiotensin-I into angiotensin-II, a potent vasopressor, and aldosterone-stimulating peptide. The enzyme is also able to inactivate bradykinin, a potent vasodilator (McKusick, 2007).

2.2 Cardiovascular diseases

2.2.1 Hypertension

2.2.1.1 Introduction

Cardiovascular disease (CVD) is responsible for one third of global deaths and is a leading and increasing contributor to the global disease burden (WHO, 2003a:1983). Hypertension is already a highly prevalent risk factor of CVD throughout the industrialised world. Worldwide hypertension is estimated to cause 7.1 million premature deaths and constitutes 4.5% of the disease burden. The proportion of global disease burden attributable to hypertension is substantial (WHO, 2003a:1983).

Despite advances in treatment, cardiovascular disease (CVD) is expected to be the leading cause of death and disability worldwide by 2020. Among risk factors for CVD, hypertension is responsible for more deaths worldwide than any other, including cholesterol, tobacco, body mass index and physical activity (Gaziano, 2005:3569).

Cardiovascular disease is rapidly becoming a major cause of morbidity and mortality in developing countries throughout the world. Hypertension is one of the major risk factors that lead to stroke, myocardial infarction, end-stage renal disease, congestive heart failure and peripheral vascular disease (Steyn *et al.*, 2001:1717).

Brown *et al.* (2003:82) mention that hypertension is one of the common causes of the global disease burden, and this problem is more likely to get worse than to improve. This is due to an ageing world population that is increasingly exposed to the determinants of raised blood pressure.

2.2.1.2 Definition

According to Lemogoum *et al.* (2003:1993) hypertension can be defined as a persistently elevated systolic and/or diastolic arterial blood pressure of 140/90mm Hg or more in subjects aged 15 years and above.

Hypertension was described by Perloff *et al.* (1993:2461) as a persistent elevation of blood pressure that exceeds an arbitrarily level set level of normalcy.

According to the Department of Health (2003:71) hypertension is a condition characterized by a blood pressure (BP) elevated above normal measured on three separate occasions, a minimum of 2 days apart.

- Systolic BP equal or above than 140mmHg

and/or

- Diastolic BP equal or above than 90mmHg

2.2.1.3 Prevalence of hypertension in South Africa

According to Steyn *et al.* (2001:1720) approximately one-fifth of the South African adult population suffer from hypertension. The overall prevalence rates, age-adjusted to the South African population for men and women are 20.9% and 21.2% respectively. When age-adjusted to the world standard, the rates for men and women are were 25.1% and 25.3% respectively. However, the rates among white (33.5%) and Asian/Indian (28%) men were higher than among white (23.3%) and Asian/Indian (25.3%) women, respectively; while African (23.5%) and Coloured (27.3%) men had lower prevalence rates than African (25%) and Coloured (29.6%) women. White males had a higher rate (33.5%), which was higher than that of white women (23.3%). White women had the lowest rates (23.3%) and Coloured women the highest rate (29.6%), after age-adjustment to world standard (see figure 2.2 and 2.3).

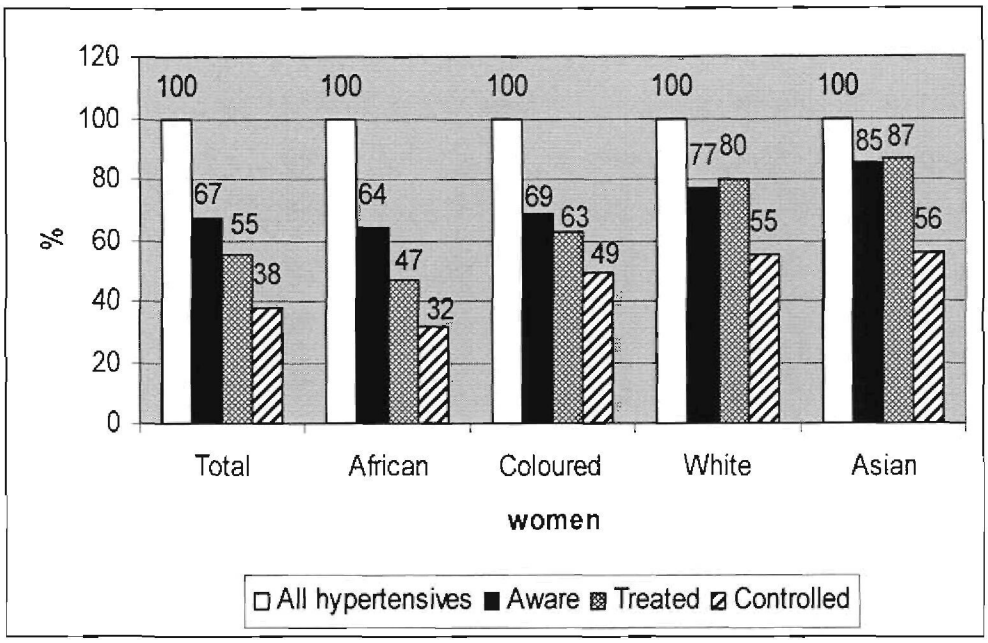


Figure 2.2: Treatment status of Hypertensive (>160/95 mm Hg and/or treatment) and controlled hypertension (160/95 mm Hg) in South African women (Adopted from Steyn *et al.*, 2001: 1723).

Steyn *et al.* (2001:1720) also mentioned that the proportion being treated with antihypertensive medication is 55% among women and 39% among men. For women, the proportion being treated also increases with age with 3% of the women aged 15 ± 24 years being treated and more than 55% of those over the age of 35 years. For men, the pattern is similar, but only reaches a level of approximately 45% being treated in those older than 45 years. More white than Asian persons with hypertension are taking antihypertensive medication for their condition than are reported being aware of having hypertension.

Thirty-eight percent of women with hypertension have a blood pressure below 160/95 mm Hg, while only 26% of these men have controlled blood pressure. Among males, Asian and Whites had the highest rate of control, 56 and 55% respectively, while only 20% of African men have controlled blood pressure. Below the age of 45 years, only 16% or less have controlled blood pressure, while the rate of control is approximately 30% for those males aged 45 years and older, For women, the younger age groups below 45 years also have less controlled hypertension than those above this range (Steyn *et al.*, 2001:1720).

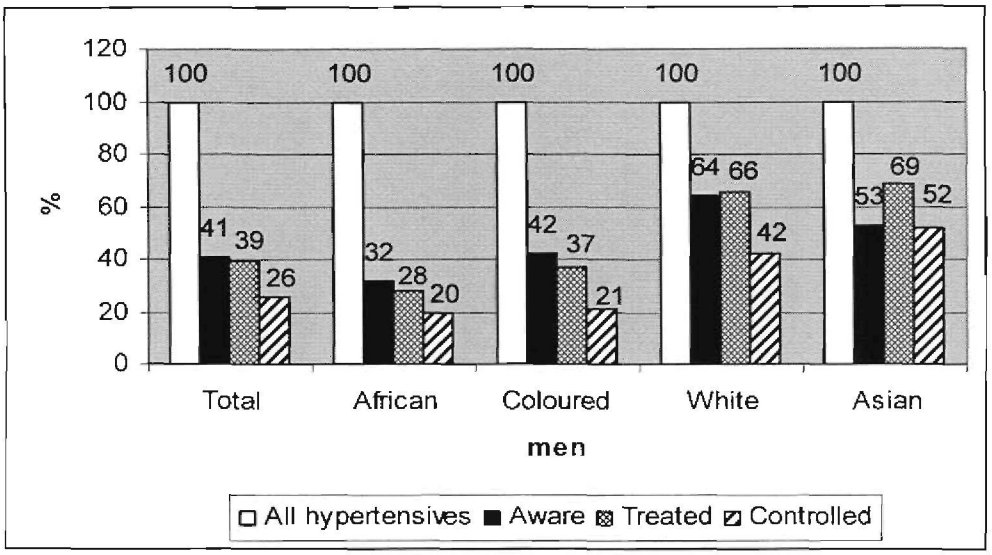


Figure 2.3: Treatment status of Hypertensive (> 160/95 mm Hg and/or treatment) and controlled hypertension (160/95 mm Hg) in South African men (Adopted from Steyn *et al.*, 2001:1723).

From this study it can be concluded that the level of treatment and awareness of the South African population is less that ideal and greater effort should be made to increase awareness and the controlling of hypertension (also see paragraph 2.2.1.16).

2.2.1.4 Physiological control of blood pressure

The main determinants of blood pressure as mentioned by Rylance (1995:190) are *cardiac output* and *peripheral resistance*. In addition, an increase in arterial blood volume increases blood pressure and a decrease in arterial blood volume lowers it. These determinants will be discussed in more detail below:

- **Cardiac output**

Cardiac output (CO) is determined by the volume of blood pumped out of the left ventricle (stroke volume) and heart rate.

CO= stroke volume x heart rate

It follows that an increase in heart rate tends to increase cardiac output and thereby increases arterial blood flow volume and blood pressure. Stroke volume is determined primarily by the strength of the heart beat, which is regulated mainly by the length of the myocardial fibres at the commencement of each contraction (Rylance, 1995:190).

- **Peripheral resistance**

Peripheral resistance is the resistance to blood flow imposed by friction between the blood and the vessel walls. Friction depends in part on blood viscosity and partly on the diameter of arterioles and capillaries. Blood viscosity depends on red cell count and plasma protein concentration. An increase in either increases viscosity and thereby tends to increase blood pressure. However, under normal circumstances blood viscosity remains fairly constant. The major factor contributing to peripheral resistance is therefore arteriole resistance, which accounts for around half the resistance in the circulatory system and which is profoundly affected by arteriole vasodilatation or vasoconstriction. The vasomotor centres, located in the medulla, can initiate vasoconstriction via sympathetic nerve fibres to maintain blood pressure and also to control the distribution of blood to areas of special need. In addition, a sudden fall in blood pressure causes aortic and carotid baroreceptors to stimulate vasoconstriction, and a sudden increase has the opposite effect. Other control mechanisms include vasomotor chemoreflexes and a medullary ischemic reflex (see figure 2.4) (Rylance, 1995:190-191).

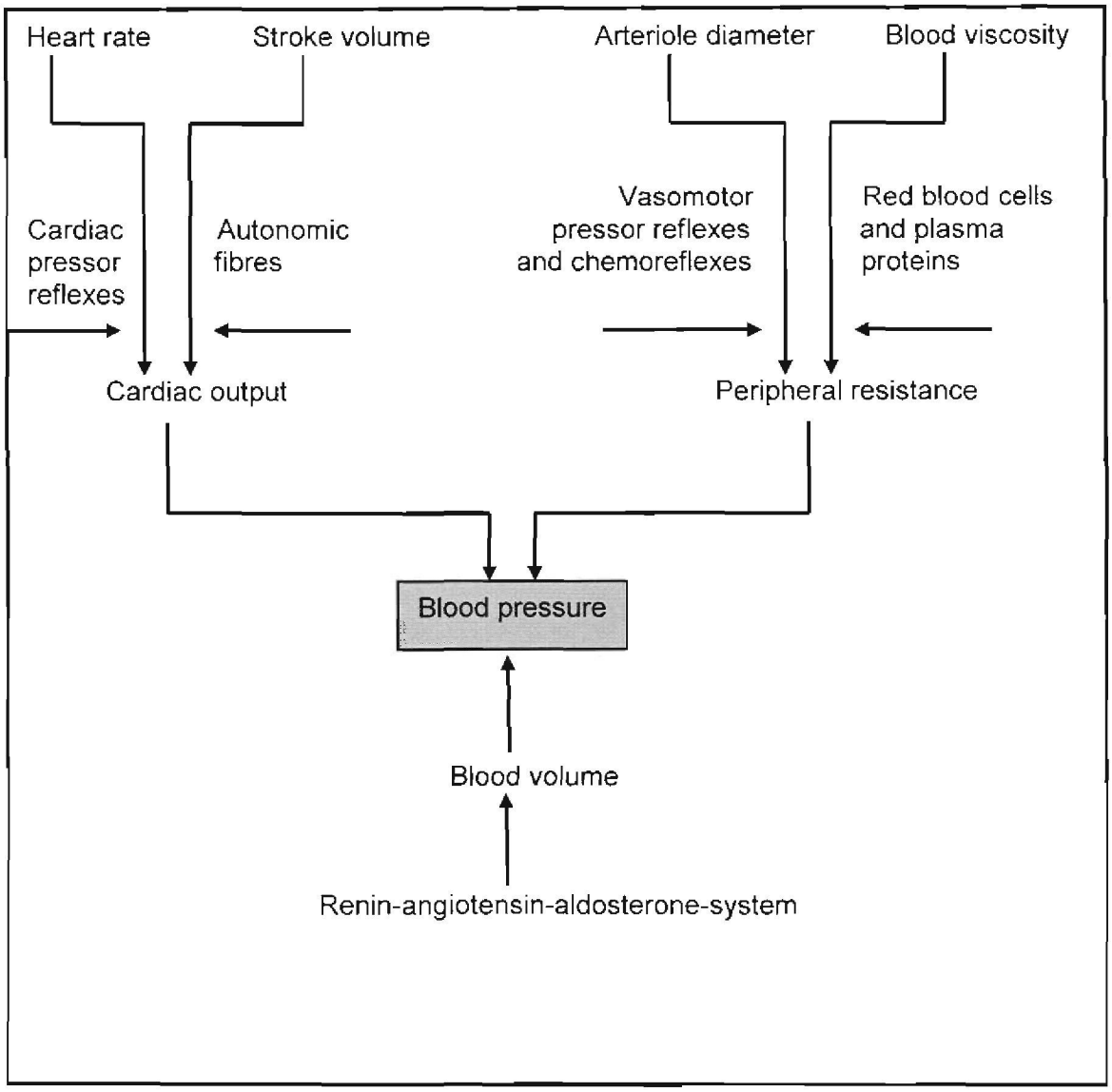


Figure 2.4: Physiological control of blood pressure (Rylance, 1995:191)

Finally, blood pressure can also be regulated by the renin-angiotensin-aldosterone system, through different mechanisms (see figure 2.5):

The renin-angiotensin-aldosterone system is a series of reactions designed to help regulate blood pressure.

1. When blood pressure falls (for systolic, to 100 mm Hg or lower), the kidneys release the enzyme renin into the bloodstream.
2. Renin splits angiotensinogen, a large protein that circulates in the bloodstream, into pieces. One piece is angiotensin I.
3. Angiotensin I, which is relatively inactive, is split into pieces by angiotensin-converting enzyme (ACE). One piece is angiotensin II, which is very active.
4. Angiotensin II, a hormone, causes the muscular walls of small arteries (arterioles) to constrict, increasing blood pressure. Angiotensin II also triggers the release of the hormone aldosterone from the adrenal glands.
5. Aldosterone causes the kidneys to retain salt (sodium) and excrete potassium. The sodium causes water to be retained, thus increasing blood volume and blood pressure.

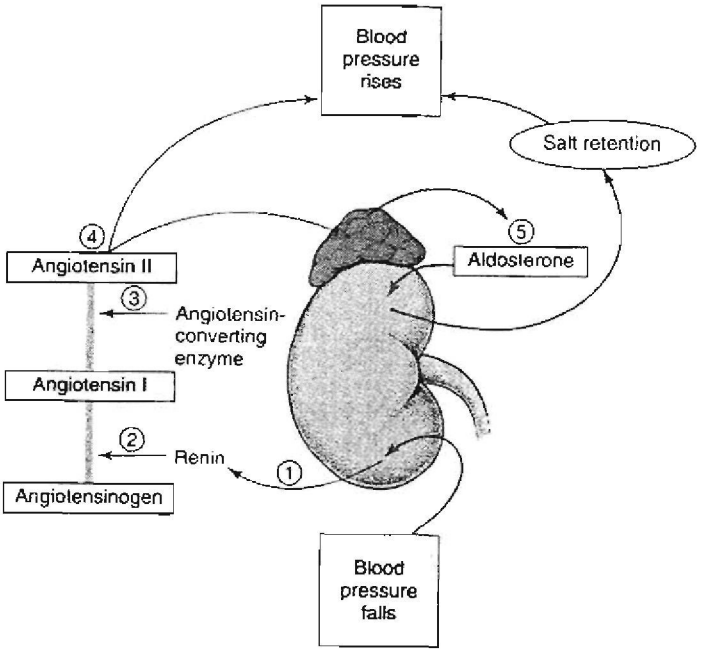


Figure 2.5: Regulating blood pressure: The renin-angiotensin-aldosterone system (Bakris, 2003:133)

2.2.1.5 Systolic blood pressure

The systolic blood pressure reflects the intermittent ejection of blood into the aorta. As blood is ejected into the aorta, it stretches the vessel wall and produces a rise in aortic pressure. The extent to which the systolic pressure rises or falls with each cardiac cycle is determined by the amount of blood ejected into the aorta with each heartbeat (*i.e.*, stroke volume and the velocity of ejection and by the elastic properties of the aorta) (Porth, 1998:364).

2.2.1.6 Diastolic blood pressure

The diastolic blood pressure is maintained by the energy that has been stored in the elastic walls of the aorta during systole. The level at which the diastolic pressure is maintained

depends on the condition of the aorta and large arteries and their ability to stretch and store energy, the competency of the aortic valve, and the resistance of the arterioles that control the outflow of blood into the microcirculation (Porth, 1998:364).

2.2.1.7 Mechanisms of hypertension

Several factors, including hemodynamic, neural, humoral, and renal mechanisms are thought to interact in producing long-term elevations in blood pressure (Porth, 1998:368). When the cardiac output rises acutely, as during sympathetic adrenergic stimulation, baroreflex adjustments tend to decrease the systemic vascular resistance, so that normal blood pressure values are regained. However, in predisposed individuals, the baroreflex control is inadequate, or the tendency to peripheral vasoconstriction is excessive, so that temporary hypertension becomes permanent. In these circumstances, sustained hypertension will result when the cardiac output is excessive, as in repetitive emotional stress, especially when associated with a tachycardia and when the systemic vascular resistance is excessive (Opie, 1992:20).

2.2.1.8 Etiology

Hypertension is a heterogeneous medical condition, and in many patients it is the result of unknown etiology e.g. essential or primary hypertension. This form of hypertension can only be controlled, but not cured. The remaining hypertension is called secondary hypertension and has a specific cause. If the cause can be identified then the hypertension can effectively be cured (Saseen & Carter, 2005:186).

There are two main types of hypertension, primary and secondary hypertension. These will briefly be discussed below:

2.2.1.8.1 Primary (essential) hypertension

Essential hypertension is the term applied to the 95% of cases in which no cause can be identified. This occurs in 10 to 15% of white adults and 20 to 30% of black adults in the United States. The onset is usually between ages of 25 and 55; it is uncommon before age 20 (Massie, 2004:401-402).

Ninety five percent of hypertension is of unknown cause, and is termed essential or idiopathic. The development of high blood pressure is often multi -factorial, and commonly not clinically obvious (Rylance, 1995:193).

- **Factors involved in the pathogenesis of essential hypertension involve the following:**

❖ **Sympathetic nervous system hyperactivity**

This is most apparent in younger hypertensives, which may exhibit tachycardia and an elevated cardiac output (Massie, 2004:402).

❖ **Defect in natiuresis**

Primary hypertension begins with an inherited defect of sodium excretion in the kidneys. This genetic defect means that the kidney requires a higher level of arterial pressure to stimulate it to secrete sodium and water; this has been described as a shift in the pressure-natiuresis-relationship (Brashers *et al.* 1998:1032).

❖ **Intracellular sodium and calcium**

Intracellular Na^+ is elevated in blood cells and other tissues in essential hypertension. This may result from abnormalities in Na^+-K^+ exchange and other Na^+ transport mechanisms. An increase in intracellular Na+ may lead to increased intracellular Ca^{2+} concentrations as a result of facilitated exchange and might explain the increase in vascular smooth muscle tone that is characteristic of established hypertension (Massie, 2004:402).

❖ **Exacerbating factors**

These are other factors that would lead to an increase in blood pressure, these include (Porth, 1998:368): Family history, age-related changes in blood pressure, race, high salt intake, obesity, hyperinsulinemia, excess alcohol intake and stress (Massie, 2004:402).

2.2.1.8.2 Secondary hypertension

Only 5% to 10% of hypertensive cases are classified as secondary hypertension (i.e., hypertension due to another disease condition). Unlike essential hypertension, many of the conditions causing secondary hypertension can be corrected or cured by surgery or specific medical treatment. Secondary hypertension trends to be seen in persons before age 30 and after the age of 50 years (Porth, 1998:373):

- **Factors that are involved in the pathogenesis of secondary hypertension include the following:**

❖ **Estrogen use**

According to Massie (2004:403) a small increase in blood pressure occurs in most women taking oral contraceptives, but considerable rises are noted occasionally. This is caused by volume expansion due to increased activity of the renin-angiotensin-aldosterone system. Only

about 5% of women who use oral contraceptives chronically will exhibit blood pressure values above 140/90mm Hg, which is twice the expected prevalence.

❖ **Renal Failure**

Disturbances in filtration and reabsorption of serum sodium, potassium, and calcium initiate the hemodynamics of early hypertension (Brashers *et al.* 1998:1033).

❖ **Primary hyperaldosteronism and Cushing's syndrome**

Patients who secrete an excess of aldosterone make up only 0.5% of all hypertensive cases. It presents as an adrenal adenoma, some patients also might have bilateral adrenal hyperplasia. (Massie, 2004:403). Glucocorticoids facilitate sodium and water retention, initiating the hemodynamics of early hypertension (Brashers *et al.* 1998:1033).

❖ **Renal vascular disease**

This cause is present in 1% to 2% of hypertensive patients. The cause in younger individuals is fibromascular hyperplasia, which is common in women under the age of 50 years (Massie, 2004:403). In addition to this, impaired blood flow and renal ischemia invoke the compensatory renin-angiotensin-aldosterone mechanism in an effort to raise the renal perfusion pressure (Brashers *et al.* 1998:1033).

❖ **Pheochromocytoma**

This tumor is most commonly located in the adrenal medulla, but can rise to other sites such as the sympathetic ganglia, where there is chromaffin tissue. Although only 0.1% to 0.5% of persons with hypertension have underlying pheochromocytoma, the disorder can cause serious hypertensive crises. Eight to ten percent of the tumors are malignant (Porth, 1998:374). The hypertension caused by pheochromocytoma is mostly episodic. Most of these patients have orthostatic falls in blood pressure, the converse of essential hypertension (Massie, 2004:403).

❖ **Hypertension associated with pregnancy**

The worsening of hypertension during pregnancy is one the most common causes of maternal and fetal mortality and morbidity (Massie, 2004:403).

❖ **Other causes**

Hypertension can also occur due to hypercalcemia, acromegaly, hyperthyroidism and also neurological disorders that cause an increase in intracranial pressure (Massie, 2004:403).

2.2.1.9 Symptoms of hypertension

Patients with uncomplicated primary hypertension are usually initially asymptomatic.

Patients with secondary hypertension usually complain of symptoms suggestive of the underlying disorder. Patients with pheochromocytoma may have a history of paroxysmal headaches, sweating, tachycardia, palpitations, and orthostatic syncope. In primary aldosteronism, hypokalemic symptoms of muscle cramps and weakness may be present. Patients with hypertension secondary to Cushing's syndrome may complain of weight gain, polyuria, oedema, menstrual irregularities, recurrent acne, or muscular weakness (Schwinghammer, 2003:84).

2.2.1.10 Lifetime risk of hypertension

Hypertension is an increasingly important medical and public health issue. The prevalence of hypertension increases with age to where half of the people aged 60-69 years in age, and about three-quarters of the people above the age of 70 years are affected. The age-related rise in systolic blood pressure (SBP) leads to the prevalence and incidence of age-related hypertension (Chobanian *et al.*, 2003:1209).

Because the lifetime risk of developing hypertension is very high, a public health strategy that compliments the hypertension treatment strategy is warranted. In order to prevent blood pressure levels from rising, primary prevention measures should be undertaken to minimize these causal factors in population, particularly in individuals with pre-hypertension. For example, it has been estimated that a 5mm Hg reduction of systolic blood pressure in a population would result in a 14% overall reduction in mortality due to stroke , a 9% reduction in mortality due to coronary heart disease, and a 7% decrease in all-cause mortality (Chobanian *et al.*, 2003:1212).

2.2.1.11 Goals of treating hypertension

According to Chobanion *et al.* (2003:1216) the ultimate health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Since the persons with hypertension, especially those older than 50 years, will reach the diastolic blood pressure goal once the systolic blood pressure goal is achieved, the primary focus should be to attain the systolic blood pressure goal. O'Brien and Bulpitt (1997:918) suggested the following in what blood pressure goals should be:

- A reasonable goal for diastolic blood pressure to be 80 to 85 mm Hg.
- A reasonable goal for systolic blood pressure to be less than 150mm Hg.

Also refer to section 2.2.1.3 for prevalence of hypertension in South Africa.

2.2.1.12 Reasons for lowering blood pressure

Chobanian et al. (2003:1216) mentioned that in clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35% to 40%; myocardial infarction, 20% to 25%; and heart failure, >50%. It is estimated that that in patients with stage 1 *hypertension (SBP 140 to 159 mm Hg and/ or DBP 90 to 99 mm Hg) and additional* cardiovascular risk factors, achieving a sustained 12 mm Hg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the presence of cardiovascular disease or target organ damage, only 9 patients would require such blood pressure reduction to prevent 1 death.

2.2.1.13 Hypertension management

Although hypertension is one of the most common medical conditions, it is unfortunately not controlled sufficiently. Estimation is that of the patients with hypertension that are not controlled, 76,9% have a systolic blood pressure of greater than or equal to 140mm Hg with diastolic blood pressure levels less than 90mm Hg (Saseen & Carter, 2005:194).

Saseen and Carter (2005:194) further added that after a patient has been diagnosed with hypertension they should be placed on both lifestyle modifications and drug therapy concurrently. Lifestyle modification alone should be considered as efficient in patients with pre-hypertension. Lifestyle modifications alone are not considered efficient in patients with blood pressure goals of less than 130/80 mm Hg, who have blood pressure values above their goal.

The non-pharmacological and pharmacological treatment will be discussed in more detail below:

2.2.1.13.1 Non- pharmacological management of hypertension

- **Lifestyle modification**

A healthy lifestyle remains the cornerstone of the management of hypertension for all levels of blood pressure. A healthy lifestyle decreases blood pressure, enhances antihypertensive drug efficacy and decreases total cardiovascular risk (Seedat *et al.*, 2006:343). In addition to that, where drug therapy may cause adverse effects and reduce the quality of life in some patients, non-pharmacological therapy has no harmful effects, improves the sense of well-being of the patient and is often less expensive (WHO, 2003a:1987).

All persons with hypertension should be encouraged to make the following lifestyle changes as appropriate:

- Maintain ideal weight (BMI<25): weight reduction in the overweight patient (BMI>25) (Milne & Pinkney-Atkinson, 2004:214).
- Salt restriction (e.g. remove the salt cellar from the table, avoid processed foods, gradually reduce added salt in food preparation), with increased potassium intake from fresh fruits and vegetables (Milne & Pinkney-Atkinson, 2004:214). Salt intake must be limited to less than 2400mg per day by consuming less than 1 tablespoon of salt per day (Seedat *et al.*, 2006:343).
- Limit alcohol intake to 2 standard drinks per day for men and 1 standard drink for women and small men. A standard drink contains about 10g of ethanol (e.g. 25ml spirits, 125ml wine, 340ml beer, 60 ml sherry, 25 ml liqueur) (Seedat *et al.*, 2006:343). Follow a prudent eating plan, i.e. low fat, fiber and unrefined carbohydrates, with adequate fresh fruit and vegetables (Milne & Pinkney-Atkinson, 2004:214). This is supported by the fact that an increase of two to seven portions daily lowers blood pressure by around 7/3 mm Hg in hypertensive patients (Williams *et al.*, 2004:152).
- Regular moderate aerobic exercise (e.g. 30 minutes brisk walking 3-5 times a week) (Milne & Pinkney-Atkinson, 2004:214). The benefit of exercise is dose-response related, and the early adaptations from a sedentary lifestyle to becoming moderately active have the greatest effect (Seedat *et al.*, 2006:343).
- Stop the use of all tobacco products. The use of snuff is common among South African women who do not smoke tobacco. Nicotine replacement should be used for patients with hypertension while under medical supervision (Seedat *et al.*, 2006:343).

2.2.1.13.2 Pharmacological management of hypertension

According to Porth (1998:372) the decision to initiate pharmacological treatment is based on the severity of the hypertension, the presence of target-organ disease, and the existence of other conditions and risk factors.

Saseen and Carter (2005:194) stated that after a definitive diagnosis of hypertension has been made, patients should be placed on both lifestyle modifications concurrently. Lifestyle modification alone is considered appropriate therapy for patients with pre-hypertension. However, lifestyle modifications alone are not considered adequate for patients with hypertension or patients with blood pressure (BP) goals of less than 130/80mm Hg (those with

diabetes and chronic kidney disease) that have BP values above their goal. The choice of initial drug therapy depends on the degree of BP elevation and the presence of compelling indications. Most patients with stage 1 hypertension should be treated initially with a thiazide-diuretic. For most patients with more severe BP elevation (stage 2 hypertension), combination drug therapy, with one of the agents preferably being a thiazide type-diuretic, is recommended. This general approach is shown in figure 2.6.

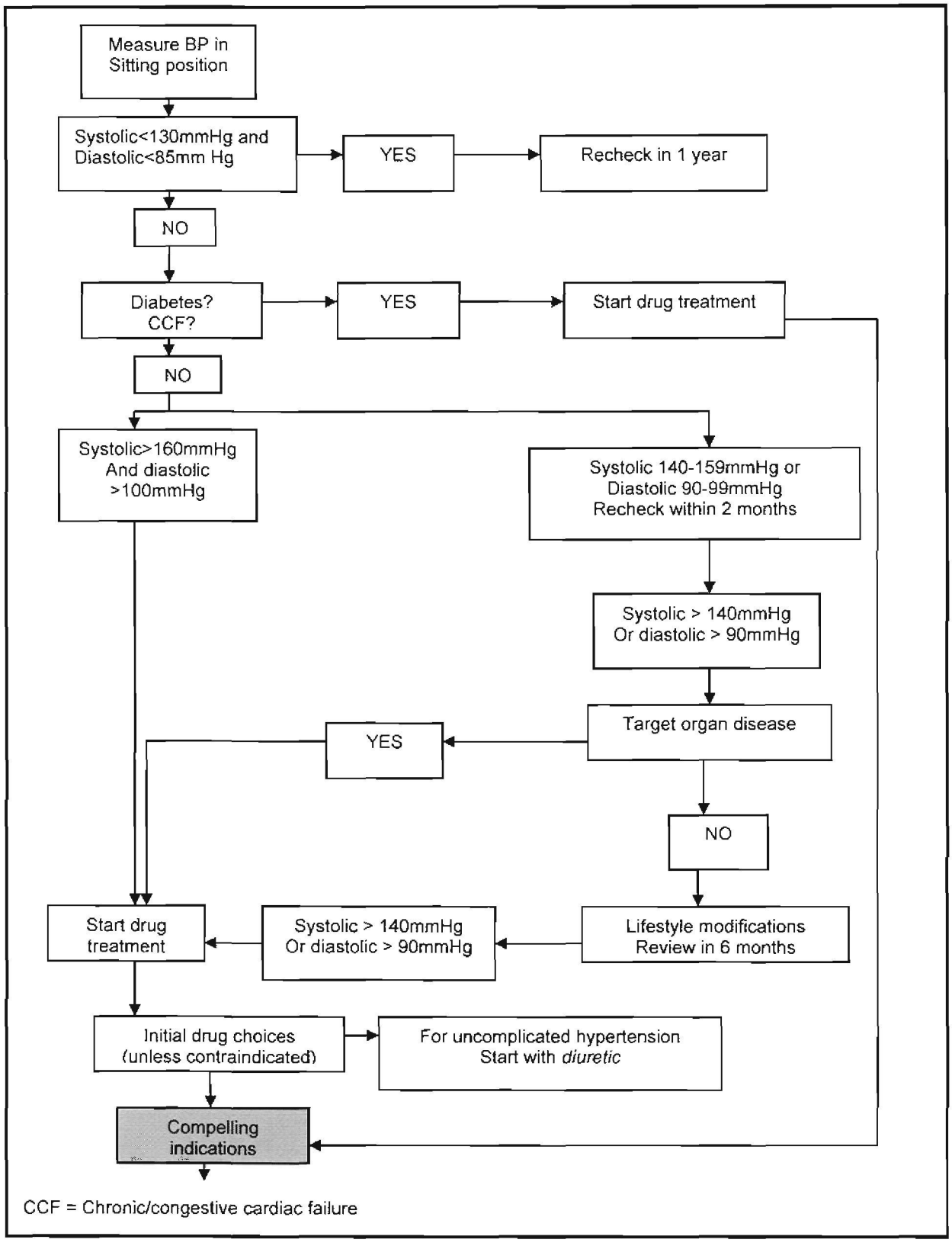


Figure 2.6: Algorithm for treating hypertension (Council for Medical Schemes, 2003)

- **Compelling indications**

Hypertension may exist in association with other conditions in which there are compelling indications for use of a particular treatment based on clinical trial data demonstrating benefits of such therapy on the natural history of the associated condition (refer to figure 2.7). Compelling indications for specific therapy involve high-risk conditions which can be a direct sequel of hypertension (heart failure, ischemic heart disease, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes, high coronary disease risk) (Chobanian *et al.*, 2003:1222).

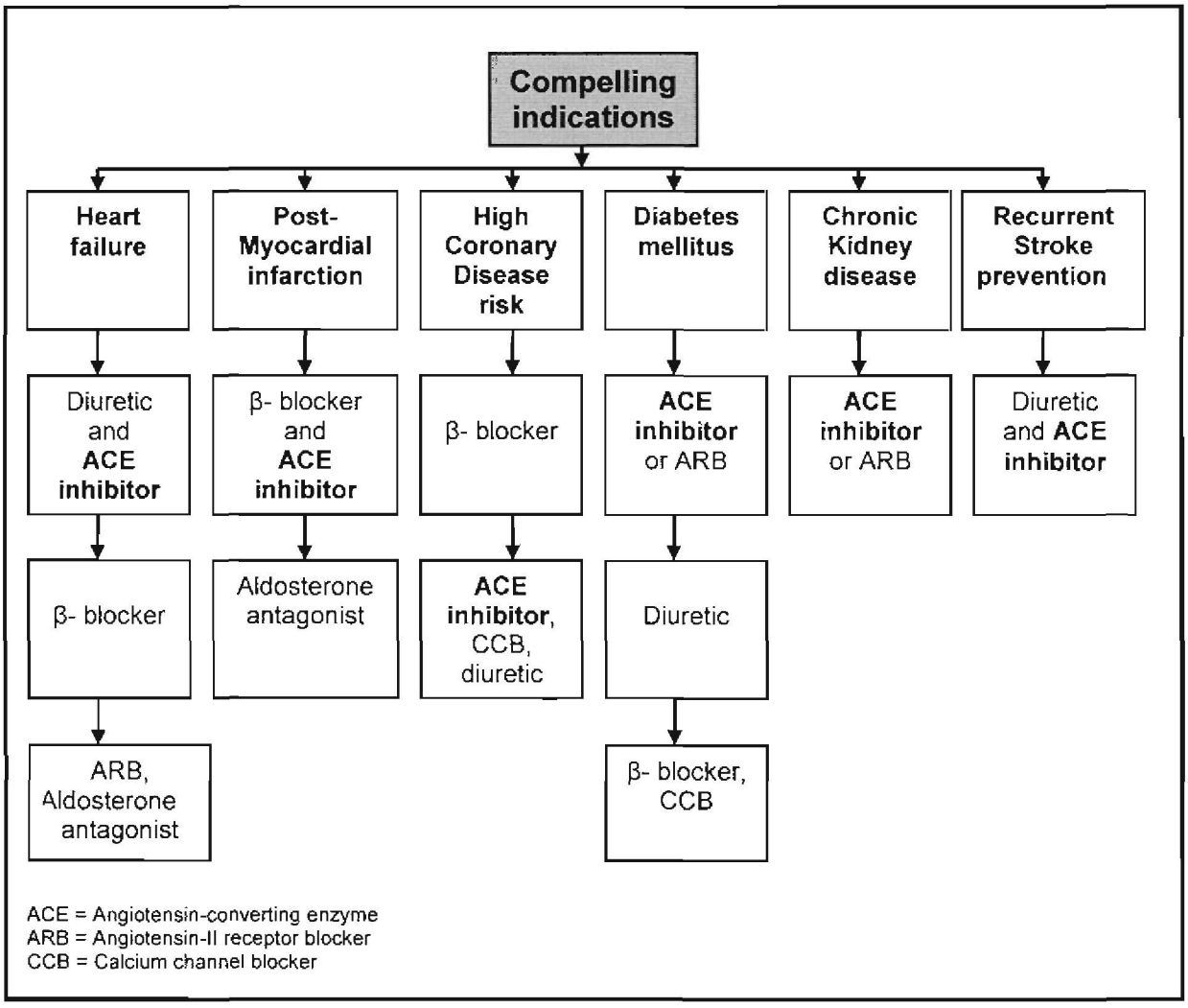


Figure 2.7: Compelling indications for individual drug classes. Compelling indications for specific drug use are evidence-based recommendations from outcome studies or existing clinical guidelines. The order of drug therapies serves only as a general guidance that should be balanced with clinical judgment and patient response. Blood pressure control should be managed concurrently with the compelling indication (Saseen & Carter, 2005:195).

Some of these compelling indications will be discussed below:

❖ **Heart failure**

Heart failure will be discussed in more detail in 2.2.2 because ACE inhibitors play an important role in the treatment of heart failure (also see 2.2.2.8.1.1).

❖ **Post myocardial infarction**

Hypertension is a strong risk factor for myocardial infarction. Once a patient experiences a myocardial infarction, controlling blood pressure is essential for secondary prevention to reduce the risk of recurrent cardiovascular events (Saseen & Carter, 2005:199). Treatment should include β-blockers and ACE inhibitors. ACE inhibitors have been shown to improve cardiac remodelling and cardiac function and to reduce cardiovascular events after myocardial infarction. The β-blockers on the other hand have shown to decrease cardiac adrenergic stimulation and also reduce the risk of a subsequent myocardial infarction or sudden cardiac death (Saseen & Carter, 2005:199).

❖ **High coronary disease risk**

Hypertensive patients are at increased risk of myocardial infarction (MI) or other major coronary events and may be at higher risk of death following an acute MI (Chobanian *et al.*, 2003:1222). Therapy is indicated toward preventing MI and death and reducing symptoms of angina and the occurrence of ischemia. Unless contraindicated, pharmacological therapy should be initiated with a β-blocker. Beta-blockers will lower blood pressure; reduce cardiac output, heart rate, and AV conduction. The reduced inotropy and heart rate decreases myocardial demand. For acute coronary syndromes, first-line therapy should consist of a β-blocker and an ACE inhibitor. This regimen will lower the blood pressure, control acute ischemia, and reduce cardiovascular risk. Diuretics can be added, if goals are not achieved with the first-line therapy (Saseen & Carter, 2005:199-200).

❖ **Diabetes mellitus**

Hypertension is an extremely common comorbid condition in diabetes and affects 20% - 60% of patients with diabetes, depending on obesity, ethnicity, and age. In type 2 diabetes, hypertension is often present as a part of the metabolic syndrome of insulin resistance also including central obesity and dyslipidemia. Hypertension in type 1 diabetes may reflect the onset of diabetic nephropathy, and increase the risk of both microvascular and macrovascular complications such as stroke, coronary artery disease, and peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy (American Diabetes Association, 2003:80S).

All patients with diabetes and hypertension should be treated with an antihypertensive regimen that includes either an ACE inhibitor or an ARB?. Both these agents should provide nephroprotection owing to vasodilation in the afferent arterioles of the kidney. Some evidence also indicates that ACE inhibitors and ARBs may increase insulin sensitivity. Beta-blockers have been shown to reduce cardiovascular risk in patients with diabetes, and should only be used when needed. Calcium-channel blockers (CCB) are useful add-on agents for blood pressure control in hypertensive patients with diabetes. Several studies have compared an ACE inhibitor with either a dihydropyridine CCB or a β-blocker. Where the ACE inhibitor was compared to the dihydropyridine CCB, the ACE inhibitor group had significantly lower rates of cardiovascular end points, including myocardial infarctions and all cardiovascular events. Based on the evidence ARBs/ ACE inhibitors are preferred first-line agents for controlling hypertension in diabetes (Saseen & Carter, 2005:200).

❖ **Chronic kidney disease**

Patients with hypertension may develop damage to either the renal tissue (parenchyma) or the renal arteries. Chronic kidney disease presents initially as microalbuminuria (30-299 mg albumin in 24 hour urine collection) that can progress to macroalbuminuria and overt kidney failure. The rate of kidney function deterioration is accelerated when both hypertension and diabetes are present (Saseen & Carter, 2005:200).

In addition to lowering blood pressure, ACE inhibitors and ARBs reduce intraglomerular pressure, which can provide additional benefits in further reducing the decline in renal function. ACE inhibitors and ARBs have been shown to reduce progression of chronic kidney disease in patients with diabetes and in those without diabetes. One of these two agents should be used as first-line therapy to control blood pressure and preserve kidney function in patients with chronic kidney disease (Saseen & Carter, 2005:201).

❖ **Recurrent stroke prevention**

The risk of clinical complications of cerebrovascular disease including ischemic stroke, hemorrhagic stroke, and dementia, increases as a function of blood pressure levels. Given the population distribution of blood pressure, most ischemic strokes occur in individuals with pre-hypertension of stage 1 hypertension. The incidence of ischemic or hemorrhagic stroke is reduced substantially by treatment of hypertension (Chobanian *et al.*, 2003:1225). Attaining goal blood pressure values in patients who have experienced a stroke is considered a primary modality to reduce the risk of a second stroke. One clinical trial, the PROGRESS[1] trial, showed that an ACE inhibitor in combination with a thiazide diuretic reduces the incidence of recurrent

1 = Perindopril Protection Against Recurrent Stroke Study

stroke in patients with a history of stroke or transient ischemic attacks. Reduction in recurrent stroke was seen with this combination therapy, even in those with blood pressure values of less than 140/90 mm Hg. These data are consistent with other evidence demonstrating reduced cardiovascular risk with ACE inhibitor therapy in high-risk patients at goal blood pressure values (Saseen & Carter, 2005:201).

2.2.1.14 Drugs used in the management of hypertension

2.2.1.14.1 Diuretics

Mechanism of action

Diuretics lower blood pressure by depleting body sodium stores. Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output (Benowitz, 2001:158).

Pharmacokinetics

All the thiazides are absorbed when given orally, but there are differences in their metabolism. Chlorothiazide, the parent of this group, is less lipid-soluble and must be given in relatively large doses. Chlorthalidone is absorbed slowly and has a longer duration of action. Although imdapamide is excreted primarily by the biliary system, enough of the active form is cleared by the kidney to exert its diuretic effect in the distal convoluted tubule (Ives, 2001:254).

Side-effects

Thiazide diuretics may cause hypokalemia, hypomagnesemia, hypercalcemia, hyperurecemia, hyperglycemia, hyperlipidemia , gout may be precipitated (Gibbon, 2003:139).

Contra- indications

Thiazides: Severe renal or hepatic impairment, hypokalemia, pre-existing hypercalcemia, hypersensitivity to thiazides or sulphonamide derivatives (Gibbon, 2003:139).

Drug interactions (Gibbon, 2005:134):

The following drug interactions can be expected with diuretics:

Potassium depleting agents (e.g. corticosteroids and amphotericin B): Increased risk of hypokalemia.

Lithium: Excretion of lithium may be substantially reduced.

NSAIDs: Increased risk of NSAID induced renal failure.

Digoxin: Diuretic-induced electrolyte disturbances.

2.2.1.14.2 Beta- adrenergic blocking agents

Mechanism of action

The exact hypotensive mechanism of β-blocking agents is unknown but may involve decreased cardiac output through negative chronotropic and inotropic effects on the heart and inhibition of renin release from the kidney (Schwinghammer, 2003:89).

Pharmacokinetics

The more lipid soluble agents are eliminated by hepatic metabolism and require a dosage reduction in patients with cirrhosis, whereas water soluble agents are mainly eliminated by the kidneys and require dosage reduction in patients with renal insufficiency. Beta blockers like pindolol, timolol, acebutolol, betaxolol and bisoprolol are partly excreted unchanged (O'Brien & Bulpitt, 1997:904).

Side-effects

Bradycardia, dizziness, drowsiness and visual disturbances to hallucinations, confusion and mental depression (usually reversed when therapy is stopped). Also gastrointestinal disturbances including nausea, diarrhea, cramps and sleep disturbances (Gibbon, 2003:146).

Contra-indications

Asthma, severe bronchospasm, second-or third-degree atrioventricular block, symptomatic heart failure, sinus bradycardia (Gibbon, 2003:147).

Drug interactions (Gibbon, 2003:146):

The following drug interactions can be expected with beta-adrenergic blocking agents:

Chlorpromazine: Mutual inhibition of hepatic metabolism of the other drug.

Cimetidine: Substantially decreases the hepatic metabolism of the beta-blocker.

Non-steroidal anti-inflammatory agents: Decreased efficacy of beta-blockers.

Digoxin, verapamil and diltiazem: Risk of additive cardiodepressant effects.

Adrenaline, amphetamines or other sympathomimetic drugs: Increased risk of hypertension.

2.2.1.14.2.1 Problems regarding β-blockers

For the first time, a new study reveals the risk of using the older drugs which are no longer recommended for treating high blood pressure. Patients taking β-blockers and diuretics- standard medication for over 30 years- are at far greater risk of becoming diabetic. Not only are

they less effective than newer medication, but they actually hasten and, in some cases, induce the disease in blood pressure patients - who are already at high risk. This means that at least 8,000 Britons taking the older drugs are getting diabetes unnecessarily each year as the result (Hope, 2006). In addition to this, researchers from the Imperial College London studied 14,000 blood pressure patients in the UK, Ireland and Scandinavia. Half of the patients were treated for high blood pressure with the beta-blocker drug atenolol, along with a diuretic, and half were treated with a newer calcium channel blocker drug called amlopdipine, along with an ACE inhibitor called perindopril. The researchers found that the group taking the calcium channel blocker and ACE inhibitor experienced a 34 percent lower rate of diabetes than the patients taking beta blockers (Diabetes in control.com, 2006).

Beta-blockers such as atenolol should no longer be prescribed for the problem, according to the guidelines from the National Institute for Clinical Excellence. Adding to this, experts stress that, for the remaining beta-blocker patients still massively outweighs the risk, so they should not suddenly stop taking them. But they also call for patients to be switched to new drugs as soon as possible (Hope, 2006).

2.2.1.14.3 Calcium-channel blocking agents

Mechanism of action

These drugs block voltage-gated "L-type" calcium channels. These calcium channels are important in cardiac and smooth muscle. By decreasing calcium influx during an action potential in a frequency- and voltage-dependent manner, these agents reduce intracellular calcium concentration and muscle contractility (Trevor *et al.*, 2002:113).

Pharmacokinetics

Although the absorption of these agents is nearly complete after oral administration, their bioavailability is reduced - in some cases markedly, because of the first-pass hepatic metabolism. These agents are all bound to plasma proteins to a significant effect (70% to 98%); their elimination half- lives vary significantly from 1.3 to 64 hours (Robertson & Robertson, 1996:772).

Side-effects

Calcium channel blockers cause constipation, oedema, nausea, flushing and dizziness. More serious effects include congestive heart failure, atrioventricular blockade and sinus node depression. These are more common with verapamil than with other dihydropiridines (Trevor *et al.*, 2002:114).

Contra-indications

Hypotension, unstable angina or acute myocardial infarction, aortic stenosis (Gibbon, 2003:151).

Drug interactions

Verapamil can increase plasma concentrations of digoxin. When used with quinidine, the calcium-channel blockers may cause excessive hypotension, particularly in patients with idiopathic hypertrophic subaortic stenosis (Oates, 1996:801).

2.2.1.14.4 Angiotensin-II receptor blocking agents

Mechanism of action

These agents block the binding of angiotensin-II to the angiotensin-I (AT_1) subtype angiotensin receptors in blood vessels and other tissues. Most of the physiological effects of the peptide are thus inhibited (Fink, 1998:189).

Pharmacokinetics

The agent is readily absorbed orally and undergoes first-pass hepatic metabolism to an active carboxylic acid metabolite that has greater activity than the parent drug, and some inactive metabolites. Bioavailability is about 35 %. The half-life of Losartan is about 1.5 – 2.5 hours, and the half-life of the active metabolite is 6 to 9 hours (Gibbon, 2003:158).

Side-effects

Dizziness and dose related orthostatic hypotension (particularly in volume depleted patients), headache, skin rash, urticaria, cough, myalgia, gastrointestinal effects (diarrhea, nausea, and dyspepsia), taste disturbance, fatigue. Hyperkalemia and raised liver enzymes may occur, and rarely, angioedema (Gibbon, 2005:152).

Contra-indications

Hypersensitivity to angiotensin-II blocking agents. They must be used with caution in patients with renal artery stenosis (Gibbon, 2003:158).

Drug interactions

Potassium-sparing diuretics or potassium supplements; these can cause hyperkalemia (Gibbon, 200:152).

2.2.1.14.5 Alpha- adrenoreceptor blocking agents

Mechanism of action

Phenoxybenzamine binds covalently to the alpha receptor, thereby producing an irreversible (insurmountable) blockade. The other agents are competitive pharmacologic antagonists (Trevor *et al.*, 2002:89).

Pharmacokinetics

These drugs are all active by the oral as well as the parenteral route, though phentolamine and tolazoline are rarely given orally. Phenoxybenzamine has a short elimination half-life but a long duration of action (48 hours). Phentolamine and tolazoline have long durations of action of 2-4 hours when used orally and 20-40 minutes when given parenterally; prazosin acts for 8 -10 hours (Trevor *et al.*, 2002:89).

Side-effects

Frequent: dizziness, postural hypotension, syncope, drowsiness, weakness, lack of energy, headache, nausea, palpitations. Less frequent: oedema, orthostatic hypotensive reaction with first dose and with subsequent dose increases (Gibbon, 2003:134).

Contra-indications

Hypersensitivity to quinazolines (Gibbon, 2005:130).

Drug-interactions

Nifedipine, other antihypertensive or nitrates. These may cause possible excessive hypotension.

2.2.1.14.6 Angiotensin-converting enzyme (ACE) inhibitors

Due to the fact that ACE inhibitors are considered the focus of this study as first line antihypertensive therapy (see 2.2.1.14.7), they will be discussed in more detail than the other antihypertensive agents.

2.2.1.14.6.1 Development of ACE inhibitors

The development of the first class of ACE inhibitors originated from the observation that various polypeptides isolated from the venom of the Brazilian snake *Bothrops jararaca* could potentiate bradykinin and inhibit ACE. Among these polypeptides, a nonapeptide inhibitor snake venom (teprotide-BPP_{5qa})SQ20881 was eventually synthesized in the laboratory and was found to be

one of the most potent and selective ACE inhibitors. Utilization of this ACE inhibitor proved the importance of the renin-angiotensin system in normal cardiovascular homeostasis, as well as the various forms of hypertension (Berecek *et al.*, 1993:191).

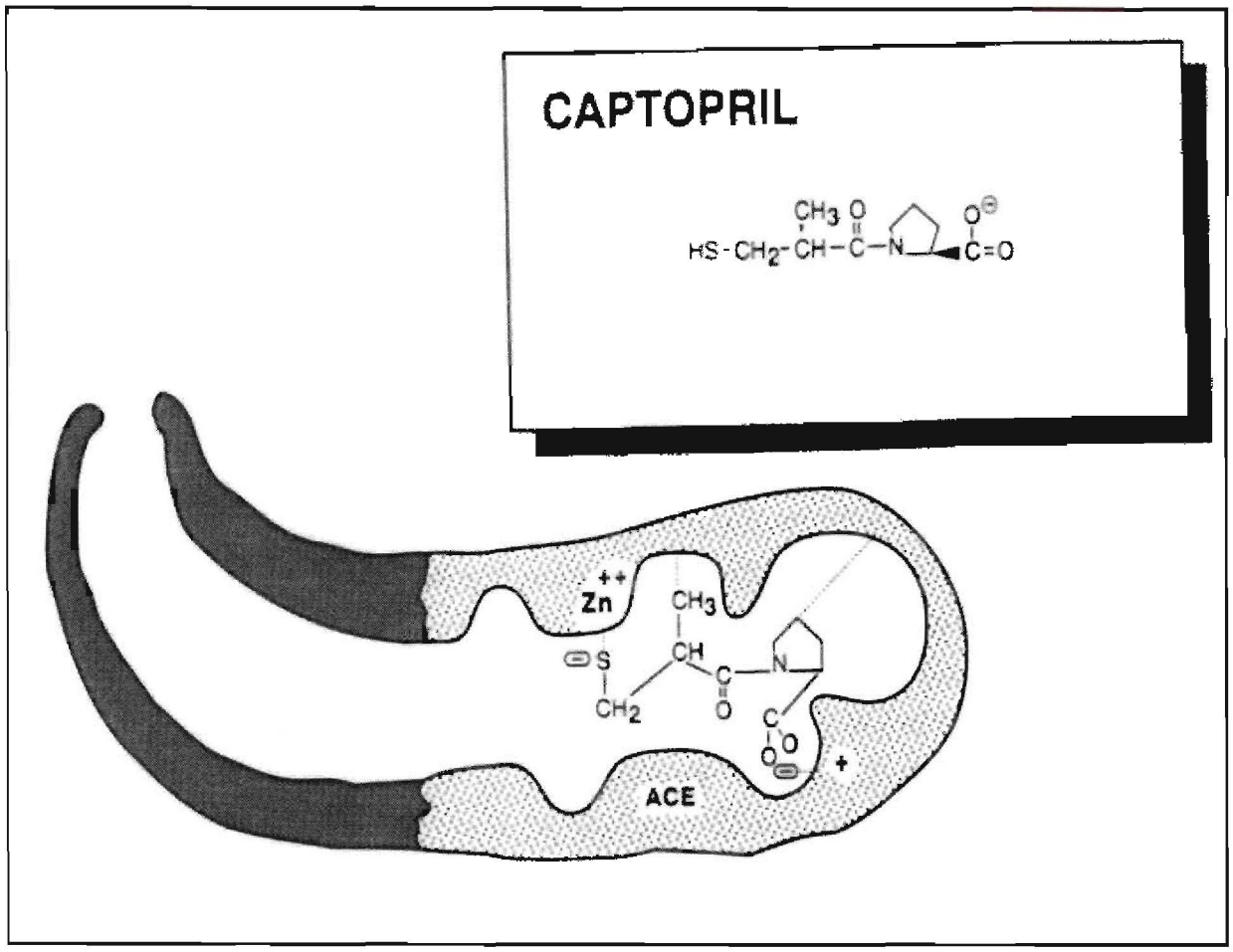


Figure 2.8: A schematic representation of the active site of ACE. The panel shows the structure of captopril and the putative binding of captopril to the active site of ACE (Berecek *et al.*, 1993:192).

The structure of captopril and the key hypothesized binding sites with ACE are shown in Figure 2.8. Addition of a sulfhydryl group into captopril increased the inhibitory potency of this compound many times over that of its chemical precursor, which contained carboxyl function, since the sulphur moiety binds tightly to the with the zinc ion of ACE. However, its sulfhydryl moiety which contributes to its potency is believed to be responsible for a number of adverse effects such as proteinuria, loss of taste, and skin rash. Therefore an effort was made to develop a nonthiol-containing ACE inhibitor (Berecek *et al.*, 1993:191-192).

2.2.1.14.6.2 Chemical classification

ACE inhibitors can be classified into three broad groups (see table 2.1):

Table 2.1: Classification of ACE inhibitors (Gibbon 2003:157)

Class	Examples of active ingredients
• **Captopril-related**	Captopril
• **Prodrugs**	Benazepril, Cilazepril, Enalapril, Fosinopril, Perindopril, Moexipril, Quinapril, Ramipril, Trandalopril
• **Water-soluble**	Lisinopril

- **Captopril-related**

Captopril

Captopril, the "*first of the ACE inhibitors*" and still the "*gold standard*", was originally thought to be a drug with a high incidence of adverse side-effects and particularly feared for serious complications such as neutropenia and renal impairment. Today, paradoxically, the drug is being promoted for its absence of side-effects and for a good "quality of life" (Opie, 1992:155).

Given orally, captopril is rapidly absorbed and has a bioavailability of about 75%. Peak concentrations in plasma occur within an hour and the drug is cleared rapidly (half life of approximately 2 hours). Most of the drug is eliminated through the urine, 40% to 50% as captopril disulfide dimers and captopril-cysteine disulfide (Jackson & Garrison, 1996:745).

- **Prodrugs**

Class II ACE inhibitors are prodrugs and must be converted by hepatic metabolism to the active form e.g. enalapril is converted to enalaprilat (Gibbon, 2003:156).

Benazepril

Cleavage of the ester moiety by hepatic esterases transforms benazepril hydrochloride (prodrug) to benazeprilat and is *in vitro* more potent than captopril, enalaprilat, or lisinopril. Benazepril is rapidly, yet incompletely (37%) absorbed after oral administration. Benazepril is

almost completely metabolized to benazeprilat and to the glucuronide conjugates of benazepril and benazeprilat which are excreted into both the urine and the bile. Peak plasma concentrations of benazepril are reached within 0.5 and 1 hour and for benazeprilat within 1 to 2 hours. Benazeprilat has an effective half-life in the plasma of 10 to 11 hours (Jackson & Garrison, 1996:746).

Cilazepril

Cilazepril is a prodrug, being converted to its active form cilazeprilat which has a long terminal half-life, with longer duration of action than enalapril. This drug is rapidly absorbed with peak plasma levels reached within 1 to 2 hours. Cilazepril is rapidly metabolized by deesterification to its active form cilazeprilat, and takes place mainly in the liver and blood (Opie, 1992:160). Almost all cilazepril has been excreted within 6 to 8 hours: there is a progressive excretion of cilazeprilat in two phases, first an early phase then a later phase from approximately 8 to 24 hours (Opie, 1992:161).

Enalapril

This compound was the first of the prodrug ACE inhibitors clinically available. Absorption is rapid with peak concentrations of unchanged enalapril reached at about 1 hour, and serum concentrations of enalaprilat is reached after 3 to 4 hours (Opie, 1992:167). Enalapril has a half-life of only 1.3 hours, but enalaprilat has a half-life of about 11 hours, because of the tight binding to ACE (Jackson & Garrison, 1996:745).

Fosinopril

Cleavage of the ester moiety by hepatic esterases transforms fosinopril (produg) to fosinoprilat that is *in vitro* more potent than captopril, yet less potent than enalaprilat. Fosinopril is nearly completely metabolized to fosinoprilat (75 %) and to the glucuronide conjugate of fosinoprilat in plasma is achieved in 3 hours. Fosinoprilat has an effective half life of 11.5 hours and the clearance is altered by renal impairment (Jackson & Garrison, 1996:746).

Perindopril

After rapid absorption from the gastrointestinal tract, perindopril (prodrug) undergoes metabolism by two pathways, chiefly by cyclization (30% to 40%) to inactive forms, but 15% undergoes hydrolysis in the liver to form perindoprilat (Opie, 1992:173). The peak plasma concentrations of perindoprilat are achieved in about 3 to 4 hours and have a terminal half-life of 27 to 33 hours or even longer (Opie, 1992:174).

Moexipril

Moexipril is another prodrug which is converted to moexiprilat by deesterification. Moexipril is incompletely absorbed, with bioavailability as moexiprilat of 13%. The time to peak concentration of moexiprilat is almost 1.5 hours, and the elimination half-life varies between 2 and 9 hours (Jackson & Garrison, 1996:746).

Quinapril

Cleavage of the ester moiety by hepatic esterases transforms quinapril hydrochloride (prodrug) into quinaprilat, which is *in vitro* about is as potent as benazeprilat. Quinapril is rapidly absorbed (peak concentrations within 1 hour), and oral absorption is about 60%. Peak concentration in plasma is reached in about 2 hours, and the initial half-life of quinaprilat is 2 hours. However, quinaprilat has a prolonged terminal half-life of 25 hours that may be due to high affinity binding to the drug to tissue ACE (Jackson & Garrison, 1996:746).

Ramipril

According to Jackson and Garrison (1996:746) ramipril is transformed to ramiprilat by hepatic esterases. Ramipril is rapidly absorbed with peak concentrations achieved within 1 hour, and the oral absorption is 50 % to 60 %. Ramiprilat is mainly excreted by the kidneys. Ramiprilat displays triphasic elimination kinetics with half-lives of 2 to 4 hours, 9 to 18 hours, and longer than 50 hours.

Trandalopril

Opie (1992:184) mentioned that trandalopril is converted to the active form, trandaloprilat, by metabolism. After fast absorption and high first-pass metabolism, trandaloprilat is rapidly formed. Approximately twice as much trandaloprilat is found in feces as in urine, suggesting a high rate of biliary elimination. After an initial fast half-life of about 3.5 hours, there is a prolonged terminal elimination phase as in the case of many other ACE inhibitors.

- **Water-soluble**

Lisinopril is the only class III ACE inhibitor. It is water soluble and not hepatically metabolized (Gibbon, 2003:157).

Lisinopril

Lisinopril is the lysine analog of enalaprilat; and unlike enalapril, lisinopril itself is active. *In vitro,* lisinopril is a slightly more potent ACE inhibitor than enalaprilat. Lisinopril is slowly, variably, and incompletely (30%) absorbed after oral administration. The peak concentrations in plasma

are achieved in about 7 hours, and it is cleared intact by the kidney and its half-life plasma is about 12 hours (Jackson & Garrison, 1996:745).

2.2.1.14.6.3 Mechanism of action of ACE inhibitors

Davies *et al.* (2000:429) stated that ACE inhibitors inhibit the production of angiotensin-II, a potent vasoconstrictor and growth promoter, and increase concentrations of the vasodilator bradykinin by inhibiting its degradation. Bradykinin has been shown to have beneficial effects associated with the release of nitric oxide and prostacyclin, which may contribute to the positive haemodynamic effects of the ACE inhibitors. ACE inhibitors also reduce the activity of the sympathetic nervous system as angiotensin-II promotes the release of noradrenaline and inhibits its uptake. In addition, they also improve β receptor density (causing their up regulation), variation in heart rate, baroreceptor function, and autonomic function (including vagal tone).

2.2.1.14.6.4 Adverse effects of ACE inhibitors

- **Hypotension**

Hypotension may be manifested as dizziness, lightheadedness, presyncope, or syncope. It occurs most commonly early in therapy or after an increase in dose, although it may occur any time during treatment (Johnson *et al.*, 2002:201).

- **Cough**

A dry, hacking cough occurs in up to 40% of patients with heart failure, independent of ACE inhibitor use, although ACE inhibitors significantly increase its incidence (Johnson *et al.*, 2002:201)

- **Hyperkalemia**

Despite some reduction in the concentration of aldosterone, significant retention of K^+ is rarely encountered by patients with normal renal function who are not taking any drugs that can cause retention of K^+. ACE inhibitors can lead to the retention of K^+ in patients taking K^+-sparing diuretics, K^+ supplements , beta-blockers, or non-steroid anti-inflammatory drugs (NSAID's) (Jackson & Garrison, 1996:750-751).

- **Acute renal failure**

ACE inhibitors can cause a reversible decline in renal function in the setting of decreased renal perfusion, whether it is due to bilateral renal artery stenosis, severe congestive heart failure, or volume depletion. The mechanism is illustrated in figure 2.9. When perfusion pressure or

afferent arteriolar pressure is decreased in the glomerulus, glomerular filtration is maintained by efferent arteriolar vasoconstriction, an effect of angiotensin-II. Blocking the formation of angiotensin-II, and increasing the formation of bradykinin, causes selective efferent arteriolar vasodilation and results in a decrease in glomerular filtration (Brown *et al.*, 1998:1415).

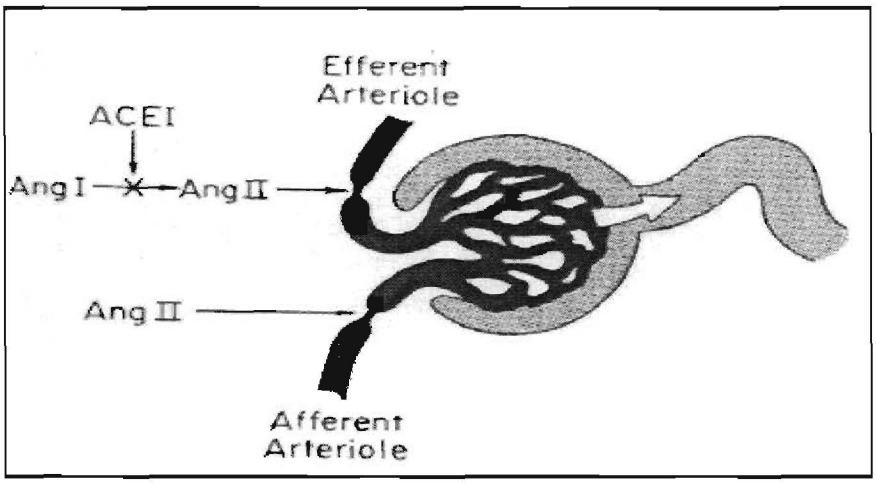


Figure 2.9: Mechanism by which ACE inhibitors can cause a decrease in glomerular filtration in setting of hypoperfusion (Brown *et al.*, 1998:1416)

- **Fetopathic potential**

Although ACE inhibitors are not teratogenic during the first trimester, continued administration of ACE inhibitors during the second and third trimesters can cause oligohydramnios, fetal calvarial hypoplasia, fetal pulmonary hypoplasia, fetal growth retardation, fetal death, neonatal anuria, and neonatal death. These effects can be due to fetal hypotension (Jackson & Garrison, 1996:750-751).

- **Skin rash**

ACE inhibitors may cause a maculopapular rash that may or may not itch. This rash may resolve itself spontaneously or with the use of antihistamines. This side effect was initially thought to come from the sulfydryl group in captopril, but this can also occur from other ACE inhibitors (Jackson & Garrison, 1996:750-751).

- **Proteinuria**

The ACE inhibitors have been associated with proteinuria. This is however not a contraindication for ACE inhibitor use, as ACE inhibitors are renoprotective in patients with

certain renal diseases associated with proteinuria (e.g. diabetic nephropathy) (Jackson & Garrison, 1996:750-751).

- **Angioneurotic oedema**

Angioneurotic oedema is a feared complication of ACE inhibitor therapy. It is more likely to occur in blacks than whites. Facial involvement is most common and only requires withdrawal of the drug (Carter & Saseen, 2002:175).

- **Dysgeusia**

An alternation in or the loss of taste can occur in patients receiving ACE inhibitors. This adverse effect, usually from captopril, is reversible (Jackson & Garrison, 1996:750-751).

2.2.1.14.6.5 *Contra-indications*

Bilateral or single kidney renal artery stenosis, history of angioedema and pregnancy (Gibbon, 2003:149).

2.2.1.14.6.6 Drug interactions

Antacids may reduce the bioavailability of ACE inhibitors; Capsaicin may worsen ACE inhibitor-induced cough; non-steroid anti-inflammatory drugs (NSAID's), including aspirin, may reduce the antihypertensive response to ACE inhibitors; and K^+ -sparing diuretics and K^+ supplements may exacerbate ACE inhibitor-induced hyperkalemia. ACE inhibitors may increase plasma levels of digoxin and lithium, and may also increase hypersensitivity reactions to allopurinol (Jackson & Garrison, 1996:751).

2.2.1.14.7 Reasons for using ACE inhibitors as first line antihypertensive therapy

ACE inhibitors have been demonstrated to be very effective therapy in all degrees of hypertension and for all age groups. They have the theoretical advantage in old people with cerebrovascular disease of shifting the cerebral blood flow autoregulatory curve downwards. Thus falls in blood pressure do not lead to falls in cerebral blood flow. They also do not interfere with either the central autonomic or peripheral nervous system; they do not have postural effects, no interference with exercise and retention of normal sexual function. Unlike other peripheral vasodilators, there is no reflex tachycardia or sympathetic stimulation (Johnston, 1989:1104).

ACE inhibitors alone normalize blood pressure in approximately 50% of patients with mild- to-moderate hypertension, and many consider ACE inhibitors first-line drugs for the treatment of high blood pressure, except for elderly African-American patients (Jackson & Garrison, 1996:747).

Furthermore, Johnston (1989:1105-1109) mentioned that ACE inhibitors have an added advantage over diuretics, because they are free from unfavourable side effects. There is no fall in plasma protein and they will partially reverse diuretic-induced hypokalemia. One of the disadvantages of more traditional antihypertensive therapy has been the failure to provide primary prevention from ischemic heart disease and decrease the incidence of acute myocardial infarction in hypertensive patients. This is now a major cause of death in essential hypertension, and it is important that future therapy be shown to provide primary protection. These favorable effects of ACE inhibitors on potassium homeostasis, sympathetic nervous function and ventricular hypertrophy all provide a physiological basis that give hope for primary reduction of ischemic heart disease in treated hypertensives. Similar claims for renoprotection have also been for the ACE inhibitors. Nevertheless, ACE inhibitors have a lot of characteristics that one would desire for first-line antihypertensive therapy.

2.2.1.15 Situations favoring the use of ACE inhibitors as first-line antihypertensive agents (Opie, 1992:53):

- Diabetic nephropathy (with or without hypertension)
  - ❖ Microalbuminuria
  - ❖ Proteinuria
- High-renin hypertension or low-renin hypertension on low salt diet.
- Presence of large vessel vascular disease
  - ❖ Loss of aortic compliance
  - ❖ Peripheral vascular disease
- Presence of left ventricular hypertrophy
- Presence of severe congestive heart failure (low test dose essential especially if over-diuresed)
- When maintenance of optimal "quality of life" is crucial
  - ❖ Exercise capacity

- ❖ Intellectual activity
- ❖ Sexual function

- When maintenance of normal metabolic status is crucial
  - ❖ Avoiding insulin resistance
  - ❖ Lipid-neutrality
  - ❖ Unaltered diabetic control

2.2.1.16 Patient education

Good patient education is essential, because then the patient will understand what the management of hypertension involves and this will lead to better patient compliance. This in return will lead to better control of the patient's blood pressure (Milne & Pinkney-Atkinson, 2004:222).

According to Milne and Pinkney-Atkinson (2004:222) the following aspects must be considered as good pharmaceutical care, and must be discussed with the patient.

- Patients must understand hypertension and the consequences associated with inappropriate treatment of the hypertension.
- Patients must be informed of their blood pressure readings, their overall cardiovascular risk and whether their blood pressure is controlled with every visit.
- Patients must inform the relevant medical authorities about their hypertension and the medications that they are using for their treatment.
- Patients must be encouraged to follow lifestyle changes e.g. reduction in weight.
- Patients should be encouraged to request the measurement of their blood pressure with every visit.
- Adverse effects must be anticipated and the therapy must be adjusted to prevent or minimize any adverse effects.
- Adherence to management must be emphasized; this is an integral part of achieving blood pressure goals.
- Patients must be asked to return any drug containers and unused drugs to measure the adherence of the therapy.

- A positive attitude must be encouraged in order to achieve the therapeutic goals, and the need to add effective drugs should be explained stepwise in sufficient doses so as to achieve these goals.
- Adherence to management should be emphasized. There must be an agreement with the patient with regard to the blood pressure goal (Chobanian *et al.*, 2003:1240).
- The patients' concerns must be discussed and misunderstandings clarified. (Chobanian *et al.*, 2003:1240).

2.2.1.17 Follow-up monitoring

Once antihypertensive drug therapy has been initiated, most patients should return for follow-up and adjustment of medications at monthly - or more frequent - intervals until the blood pressure goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. When the blood pressure goal has been reached and is stable, follow-up visits can usually be at 3- to 6- month intervals (Chobanion *et al.*, 2003:1222). Patients should be monitored routinely for adverse drug effects. These adverse effects should typically occur within 2 to 4 weeks after starting a new agent, or increasing the dose. Additional monitoring may be needed for other concomitant diseases (e.g. dyslipididemia, and gout). The occurrence of an adverse drug effect may require dosage reduction or substitution with an alternatively antihypertensive agent (Saseen & Carter, 2005:214).

2.2.1.18 Shortcomings and problems in the treatment of hypertension

Patients, despite filling their prescriptions, do not take their medications according to instructions. Physicians often are not sufficiently aggressive in adjusting antihypertensive therapy to achieve meaningful blood pressure reductions. It is also likely that despite the wide variety of drugs available for the treatment of hypertension, it remains difficult to bring the blood pressure down to acceptable levels. Although most drugs can work effectively against the primary mechanisms of hypertension, compensatory mechanisms are frequently activated and these prevent optimal blood pressure responses (Weber, 1998:146S).

One way of combating this problem is to use effective combination therapy (discussed in 2.3) and generic medications (discussed in 2.4) (Moore, 2005:27). These shortcomings will be discussed in more detail below:

- **Noncompliance with therapy**

Patient compliance still remains the most important reason for poor compliance rates (Neutel *et al.*, 2001:286). Noncompliance by patients has been attributed to a lack of the understanding of the consequences of their untreated hypertension, attitudes of indifference, side-effects of the antihypertensive medication, inconvenient dosage regimens, or a combination of the above factors. Patients must be educated in the consequences of not taking their prescribed medications (Julius, 2000:59S).

- **Insufficiently aggressive treatment**

The other possibility for the failure in achieving blood pressure control in the majority of patients is that physicians are not aggressive enough in the treatment of the patient with hypertension. Because the consequences of inadequately controlled blood pressure are potentially grave, the physician should not hesitate before switching to another drug or using combination therapy by adding other agents as necessary (Julius, 2000:59S).

- **Concern over adverse events or negative metabolic consequences**

Physicians are frequently in the position that they have a patient whose blood pressure has improved on the initial treatment, but is not adequately controlled. Increasing the dose of the initial treatment may provide adequate blood pressure control, but is associated with a significant increase in dose-related side- effects, which then has a negative effect on patient compliance (Neutel *et al.*, 2001:287).

- **Cost**

Frequently adding a second drug or increasing the dose of a drug will have a major impact on cost. Physicians will rather accept inadequate control rather than titrating in patients in whom cost is an issue (Neutel *et al.*, 2001:287).

2.2.1.19 Hypertension in children

Hypertension is an important and detectable clinical problem in children and adolescents (Falkner & Sadowski, 1995:106S).The prevalence of hypertension in children is on the increase, and is due to the increasing prevalence of childhood obesity as well as growing awareness of this disease. There is also evidence that childhood hypertension can lead to adult hypertension (Luma & Spiotta, 2006:1558). Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Renal parenchymal disease is the most common (60 to 70 percent) cause of hypertension. Adolescents usually have primary or essential hypertension, making up 85 to 90 percent of cases (Luma & Spiotta, 2006:1560).

Essential hypertension is rarely found in children younger than 10 years and this is a diagnosis for exclusion. Significant risk factors for essential hypertension include family history and increasing body mass index (BMI). Essential hypertension is often linked to other risk factors that make up metabolic syndrome and can lead to cardiovascular disease (Luma & Spiotta, 2006:1560).

Secondary hypertension is more common in children than in adults. It can be present in adolescents, especially if they have physical findings not typically seen with essential hypertension. Renal disease is the most common cause of secondary hypertension in children (Luma & Spiotta, 2006:1560).

As with adults, the severity of hypertension in childhood can range from mild to very severe. In the presence of severe hypertension, children have morbidity and mortality similar to that of adults (Falkner & Sadowski, 1995:106S). Hypertension is also a known risk factor for coronary artery disease (CAD) in adults, and the presence of childhood hypertension is a contributing factor to the early development of coronary artery disease (Luma & Spiotta, 2006:1558).

2.2.1.19.1 Management

Treatment of hypertension in children is not designed to reduce blood pressure to any specific level, as it is in adults, because normal blood pressure varies according to age and body size during the first decades of life. Therefore, the goal of antihypertensive therapy is to achieve a level of blood pressure equal to or lower than the 95th percentile of normal blood pressure distribution according to age, height and sex of the patient (Prineas & Sinaiko, 1994:750).

Non-pharmacological therapy in children consists of weight reduction, exercise and dietary intervention. It is recommended for initial therapy in children with mild to moderate hypertension and may be of benefit for some children with a blood pressure in the high-normal range (Prineas & Sinaiko, 1994:760). When children and adolescents have been unresponsive to non-pharmacological therapy, are symptomatic, have severe hypertension, or have evidence of end-organ damage, pharmacological intervention is indicated (Falkner & Sadowski, 1995:109S)

Reasons to initiate antihypertensive medication in children and adolescents include symptomatic hypertension, end-organ damage (e.g. Left-ventricular hypertophy, retinopathy, proteinuria). Drug therapy is always an adjunct to nonpharmacological measures (Luma & Spiotta, 2006:1564). Converting enzyme inhibitors have been used successfully in children of all ages, with a minimum of adverse effects (Prineas & Sinaiko, 1994:761).

2.2.1.20 Hypertension in the elderly

Hypertension becomes more prevalent with increasing age, mostly because of reduced arterial compliance. As many as 90 percent of normotensive elderly adults develop stage 1 hypertension. Reducing blood pressure in the older adults prevents stroke, myocardial infarction, heart failure, as well as renal failure. Elderly patients with hypertension have a higher absolute risk of cardiovascular events than younger persons with hypertension and are more likely to have higher systolic blood pressure and a higher pulse pressure (increasingly recognized as an independent risk factor for cardiovascular events) (Magill *et al.*, 2003:856).

2.2.1.20.1 Management

Lifestyle measurements should be offered to all older people with hypertension and are just as effective as they are in younger people (Williams *et al.*, 2004:161).

If an elderly patient has no concomitant conditions for which an alternative medication might be helpful, diuretics are most effective and least expensive and have minimal side-effects. Patients with a history of myocardial infarction or angina should start with beta-blocker and ACE inhibitor therapy. Patients with chronic renal disease should start with an ACE inhibitor or angiotensin-receptor blocker. Patients with diabetes should start with an ACE inhibitor, angiotensin-receptor blocker, thiazde-diuretic, or a beta blocker. Recent evidence also suggests that, compared with diuretics, ACE inhibitors produce better outcomes in elderly patients, especially men (Magill *et al.*, 2003:857). Combination therapy with two or more drugs is generally needed to achieve optimal blood pressure (Chobanian *et al.*, 2003:1230).

2.2.1.21 Hypertension in blacks

Hypertension, defined by the cut-off point 140/90 mm Hg or treatment, is 50 % more common among blacks than whites or Hispanics, whereas it is twice as common using the definition of 160/90 mm Hg or treatment (Cooper & Rotimi, 1997:805). Hypertension is known to occur more frequently in the black population and is associated with a higher incidence of cerebrovascular and renal complications. This includes strokes that are more common in black hypertensive patients, and hypertension associated end-stage renal failure that is up to 20 times more likely to occur in black patients, compared to non-blacks (Gibbs *et al.*, 1999:187). In addition to this there is a greater tendency to develop left-ventricular hypertrophy (LVH); black patients with mild hypertension have a two-fold higher prevalence of LVH when compared to non-blacks with comparable blood pressure levels (Gibbs *et al.*, 1999:188).

2.2.1.21.1 Management

This population has an increased need for combination therapy to attain blood pressure goals. Lifestyle modifications are recommended to facilitate drug therapy. Blood pressure lowering effects of antihypertensive classes vary in African-Americans. Monotherapy with β-blockers, ACE inhibitors, or angiotensin-receptor antagonists (ARBs) result in less blood pressure lowering compared to Caucasian patients. This may be due to the low-renin pattern of hypertension. Even with these three classes of drugs, β-blockers may have better effects on target organ disease than ARBs. Thiazide-diuretics and calcium-channel blockers (CCB) seem to be particularly effective at lowering blood pressure in African-Americans. When either of these two classes (especially thiazide diuretics) is used in combination with a β-blocker, ACE inhibitor or ARB, the antihypertensive response is significantly increased (Saseen & Carter, 2005:203).

2.2.1.22 Refractory (resistant) hypertension

Hypertension is termed refractory when the therapeutic plan of the patient consists of more than three drugs (including thiazide diuretics) of different classes in adequate doses, and has failed to lower the blood pressure to under 140/90mm Hg in patients with essential hypertension. This is also possible if there is failure to lower the systolic blood pressure below 140mmHg in patients with isolated systolic hypertension. In these situations, referral to a specialist should be considered (Lemogoum *et al.,* 2003:1998).

According to Milne and Pinkney-Atkinson (2004:223) the term refractory hypertension can be used when the therapeutic plan has included lifestyle measures and combination therapy in adequate doses (triple-drug regimen including a diuretic), yet has failed to lower the blood pressure to below 160/95mm Hg.

Possible causes of refractory hypertension include (Milne & Pinkney-Atkinson, 2004:223):

- Unsuspected secondary cause (e.g. coartation, renal or endocrine causes)
- Poor adherence to therapeutic plan.
- Continued intake of drugs that raise blood pressure (e.g. non-steroidal anti-inflammatory drugs).
- Failure to modify lifestyle including (e.g. weight gain, heavy alcohol intake)
- Volume overload due to (e.g. Inadequate diuretic therapy, progressive renal insufficiency)

If resistant hypertension persists after remediable causes have been identified and corrected, a concerted search for a secondary cause should be conducted. If resistance still persists, consultation with a hypertension specialist is the logical next step. The specific causes can usually be identified by appropriate evaluation, and be treated effectively (Chobanian *et al.*, 2003:1230).

2.2.2 Congestive heart failure

2.2.2.1 Definition

Heart failure (HF) is a pathophysiological state in which the heart is unable to pump blood at a rate sufficient to the metabolic needs of the body (Schwinghammer, 2003a:56).

Hunt *et al.* (2005:1119) defined heart failure as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject with blood.

2.2.2.2 Prevalence of heart failure

Heart failure is a major and growing public health problem in the United States. Approximately 5 million patients in the United States have heart failure, and more than 550 000 patients are diagnosed with heart failure for the first time each year. This disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year. From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810 000 to over 1 million for heart failure as a primary diagnosis, and from 2.4 to 3.6 million for heart failure as a primary or secondary diagnosis. In 2001, nearly 53 000 patients died of heart failure as a primary cause (Hunt *et al.*, 2005:1117-1118).

2.2.2.3 Classification of heart failure

The four stages of hypertension include (Hunt *et al.*, 2001:2997):

- Stage A: Identifies the patient who is at high risk of developing heart failure, but has no structural disorder of the heart.
- Stage B: Refers to a patient who has a structural disorder of the heart, but who has never developed symptoms of heart failure.

- Stage C: The patient with past or current symptoms of heart failure associated with underlying structural heart disease.
- Stage D: Patients with end-stage disease who require specialized treatment strategies.

These stages are discussed in more detail in table 2.2.

Table 2.2: Stages of Heart Failure (Hunt *et al.*, 2001:2997)

Stage	Patient characteristics	Examples
A	High risk of developing heart failure because of the presence of conditions that are strongly associated with the development of heart failure. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of heart failure.	Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy.
B	Patients who have developed structural heart disease that is strongly associated with the development of heart failure but who have never shown signs or symptoms of heart failure.	Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.
C	Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease.	Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of heart failure.

Table 2.2 (continued): Stages of Heart Failure (Hunt *et al.*, 2001:2997)

Stage	Patient characteristics	Examples
D	Patients who have advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions.	Patients who are frequently hospitalized for heart failure or cannot safely be discharged from the hospital; patients in hospital awaiting heart transplantation; patients at home receiving continued intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of heart failure.

2.2.2.4 Pathophysiology

Heart failure can result from many cardiac diseases or disorders that alter systolic function, diastolic function, or both (Schwinghammer, 2003a:56).

Causes of systolic dysfunction (decreased contractility) are dilated cardiomyopathies, ventricular hypertrophy, and reduction in muscle mass (e.g. myocardial infarction). Ventricular hypertrophy can be caused by pressure overload (e.g. systemic or pulmonary hypertension, aortic or pulmonic valve stenosis) or volume overload (e.g. valvular regurgitation, shunts and high output-states (Schwinghammer, 2003a:56).

The causes of diastolic dysfunction are increased left ventricular hypertrophy, commonly resulting from hypertension, but conditions such as hypertrophic or restrictive cardiomyopathy, diabetes, and pericardial disease can produce the same clinical picture (Massie & Amidon, 2004:372).

2.2.2.5 Renin-angiotensin-aldosterone system in heart failure

Stimulation of the renin-angiotensin-aldosterone system leads to increased concentrations of renin, plasma angiotensin-II, and aldosterone. Angiotensin-II is a potent vasoconstrictor of the renal (efferent arterioles) and systemic circulation, where it stimulates the release of noradrenaline from sympathetic nerve terminals, inhibits vagal tone, and promotes the release of aldosterone (see figure 2.10, below). This then leads to retention of sodium and water and the increased excretion of potassium. Angiotensin-II, also has important effects on the cardiac myocytes and may contribute to the endothelial dysfunction that is observed in chronic heart failure (Jackson *et al.*, 2000:167).

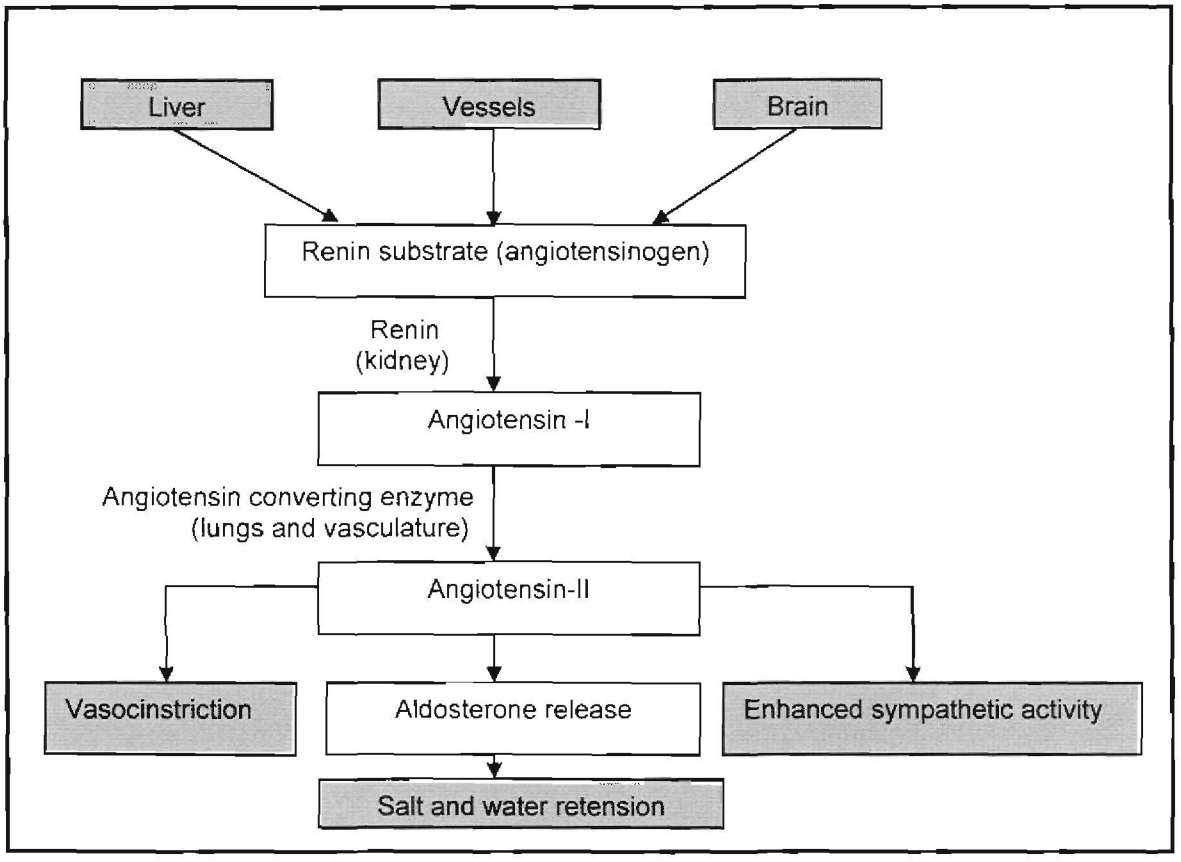


Figure 2.10: Renin-angiotensin-aldosterone axis in heart failure (Jackson *et al.*, 2000:167).

2.2.2.6 Signs and symptoms of heart failure

The signs and symptoms of heart failure are summarized in table 2.3.

Table 2.3: Symptoms and signs of heart failure (Schwinghammer, 2003a:57):

Symptoms	Signs
Right Ventricular Dysfunction	
Abdominal pain	Peripheral oedema
Anorexia	Jugular venous distension
Nausea	Hepatojugular reflux
Bloating	Hepatomegaly
Constipation	
Ascites	
Left Ventricular Dysfunction	
Dyspnea on exertion	Bibasilar rales
Paroxymal nocturnal dyspnea	Pulmonary oedema
Orthopnea	S_3 gallop
Tachypnea	Pleural effusion
Cough	Cheyne-Stokes respiration
Hemotysis	
Non-specific Findings	
Exercise intolerance	Tachycardia
Fatigue	Pallor
Weakness	Cyanosis of digits
Nocturia	Cardiomegaly
CNS symptoms	
CNS= Central Nervous System	

2.2.2.7 Goals in treatment of heart failure

The therapeutic goals for chronic heart failure are to improve symptoms and quality of life, reduce hospitalizations, slow disease progression, and prolong survival (Schwinghammer, 2003a:57).

2.2.2.8 Management of heart failure

Hunt *et al.* (2005:1120) mentioned that the development of heart failure can be characterized by considering 4 stages of the disease. The staging system recognizes that heart failure, like coronary artery disease, has established risk factors and structural prerequisites; that the development of heart failure has asymptomatic and symptomatic phases; and that specific treatments targeted at each stage can reduce the morbidity and mortality of heart failure (refer to figure 2.11).

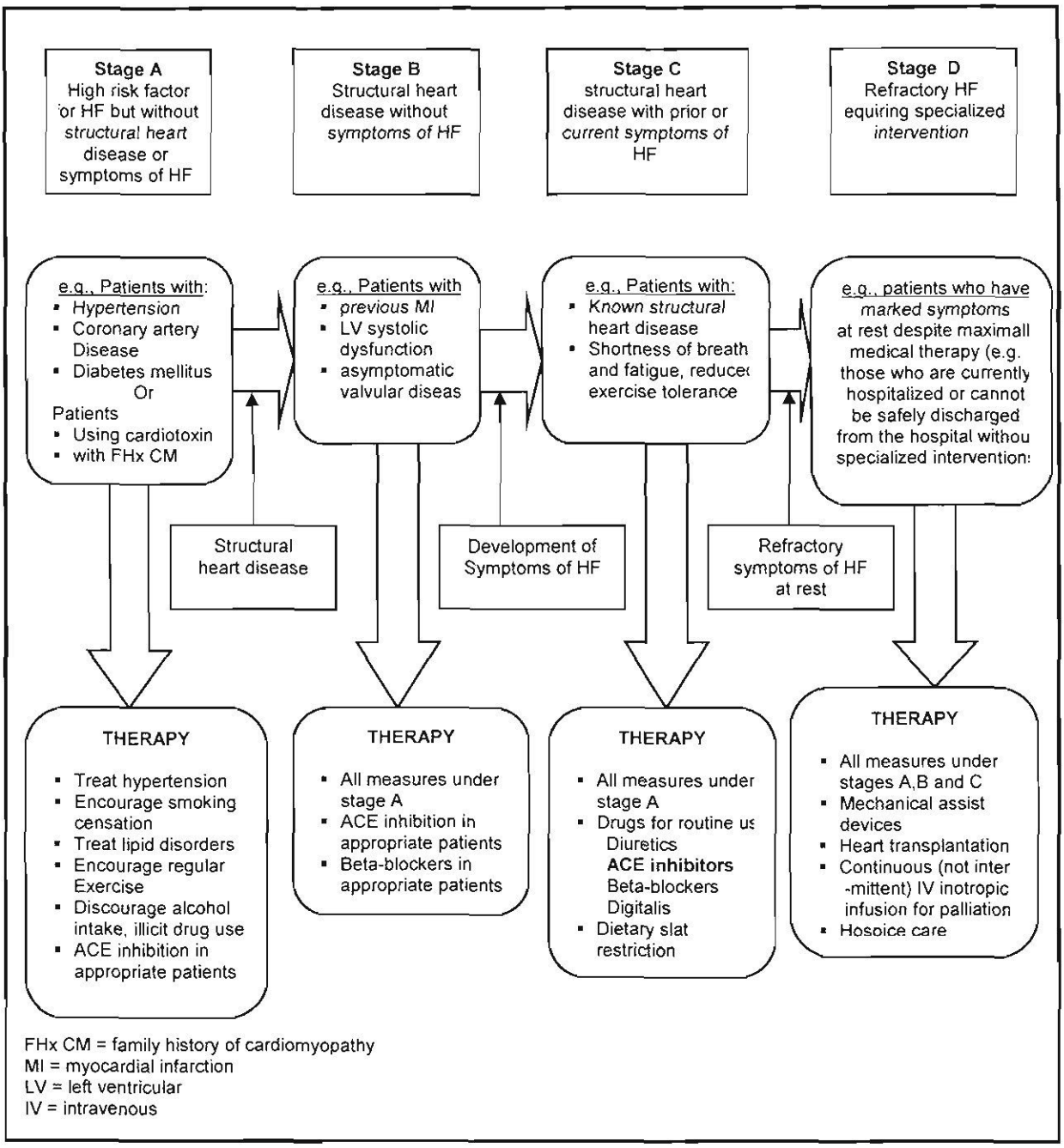


Figure 2.11: Stages in the evolution of heart failure and recommended therapy by stage (Hunt *et al.*, 2001:2999)

2.2.2.8.1 Drugs used in the management of heart failure

2.2.2.8.1.1 *ACE inhibitors*

ACE inhibitors are the cornerstone of pharmacotherapy of patients with heart failure (Johnson *et al.*, 2002:201). ACE inhibitors reduce mortality by approximately 20% in patients with symptomatic heart failure and have also been shown to prevent hospitalization, increase exercise tolerance, and reduce symptoms in these patients (Massie & Amidon, 2004:377).

As a result, ACE inhibitors should be part of first-line treatment of patients with symptomatic left ventricular systolic dysfunction (ejection fraction < 40 %), usually in combination with a diuretic. They are also indicated for the management of patients with reduced ejection fractions without symptoms, because they prevent the progression to clinical heart failure (Massie & Amidon, 2004:377).

Dosages

The therapeutic doses of ACE inhibitors for congestive heart failure are summarized in Table 2.4.

Table 2.4: Dosages of ACE inhibitors in congestive heart failure (Gibbon, 2003:157):

Drug	Congestive heart failure (CHF)	
	Initial dose	Maintenance dose
Class I: Captopril-like		
Captopril	6,25 mg	25-50 mg 3 times a day
Class II: Prodrugs		
Benazepril	2,5 mg	up to 20 mg daily
Cilazepril	-	-
Enalapril	2,5 mg	up to 10 mg twice a day
Fosinopril	-	-
Perindopril	2 mg	4 mg daily
Quinapril	2,5 mg – 5 mg	up to 20 mg twice a day
Ramipril	2,5 mg	2,5 mg – 5 mg twice a day
Trandalopril	-	-
Class III: Water-soluble		
Lisinopril	2,5 mg	5 – 20 mg daily

2.2.2.8.1.2 Diuretics

Their mechanism of action in heart failure is to reduce salt and water retention, thereby reducing ventricular preload. The reduction in venous pressure has two useful effects: reduction in oedema and its symptoms and reduction of cardiac size, which leads to improved efficacy of pump function (Katzung & Parmley, 2001:209).

2.2.2.8.1.3 Beta-blockers

Although beta-blockers have traditionally been considered contraindicated in patients with heart failure because they may block the compensatory actions of the sympathetic nervous system, there is now, however, strong evidence that these agents have important beneficial effects in this patient population. The mechanism of this benefit remains unclear, but it is likely that chronic levels of catecholamines and sympathetic nervous system activity cause progressive myocardial damage, leading to worsening left ventricular function and dilation. The primary evidence for this hypothesis is that over a period of 3 – 6 months, beta-blockers produce constant substantial rises in ejection fraction and reductions in left ventricular size and mass (Massie & Amidon, 2004:378).

2.2.2.8.1.4 Digitalis

Although the digitalis glycosides were once the mainstay of congestive heart failure treatment, their use in patients who are in sinus rhythm has declined, because they lack the benefits of the neurohormonal antagonists on prognosis and because safety concerns persist. However, their efficacy in reducing the symptoms of heart failure has been established in at least four multicentre trials which have demonstrated that digoxin withdrawal is associated with worsening symptoms and signs of heart failure, more frequent hospitalization for decompensation, and reduced exercise tolerance (Massie & Amidon, 2004:379).

Mechanism of action

Inhibition of Na^+/K^+ ATPase of the cell membrane by digitalis is well-documented and is considered to be the primary biochemical mechanism of action (Trevor *et al.*, 2002:121).

Pharmacokinetics

Bioavailability varies between 60% and 80% for tablets. The half-life is between 32 and 48 hours, prolonged in renal failure to 80-120 hours, and 0.5 – 2.0 hours (oral). The elimination is mainly renal and 50% – 70% of the drug is unchanged (Gibbon, 2005:114).

Drug interactions (Gibbon, 2003:117)

Quinidine, amiodarone, verapamil, diltiazem, spirinolactone, chloroquine and trimethoprim: May increase digoxin levels sustainability and reduce digoxin requirements.

Verapamil, beta-blockers: Additive depressant effect on AV nodal conduction and increased risk of heart block.

Potassium-sparing diuretics: Digoxin levels increased by about 20%.

Potassium-depleting agents: May potentiate digoxin toxicity by causing hypokalemia.

2.2.2.9 Goals for treating heart failure

The therapeutic goals for chronic heart failure are to improve symptoms and quality of life, reduce hospitalizations, slow disease progression, and prolong survival (Schwinghammer, 2003a:57).

2.2.2.10 Prognosis of heart failure

Massie and Amidon (2004:373) mentioned that heart failure carries a poor prognosis, once manifested. The 5-year survival rate is less than 50% overall. Mortality rates vary from < 5% per year in those with no or few symptoms to > 30% per year in those with severe and refractory symptoms. In general, men have a poorer prognosis than women because they are more likely to have coronary artery disease, which is associated with a higher mortality rate and less likely to have diastolic heart failure, which has a lower mortality rate. These figures emphasize the critical importance of early detection and intervention. The prognosis of heart failure has improved in the last two decades, probably at least in part because of the more widespread use of ACE inhibitors and beta-blockers, which markedly improves survival.

2.3 Combination therapy for the treatment of hypertension

The principle of polypharmacy has gained almost universal acceptance for those patients with certain conditions, such as angina, that do not respond to a single agent. Moreover, the treatment of hypertension often includes the use of combination therapy (addition of a drug with a complementary mechanism of action to another drug) to enhance the blood pressure lowering effect of a single agent. Although this is a widely accepted practice in medicine, the concept of polypharmacy using fixed-dose combination therapy has been slow to gain widespread acceptance (Epstein & Bakris, 1994:1969).

The use of combination therapy as the first-line treatment may provide a solution to many of the most important problems faced in the management of hypertension. If in access of 60% of patients will ultimately end up with a combination therapy, they may be better off starting with combination therapy. There are no good reasons not for using combination therapy as first-line treatment and it may be argued that it is a better approach than the stepped care approach (Neutel *et al.*, 2001:291).

2.3.1 Evolution of combination therapy

Epstein and Bakris (1994:1969) mentioned that historically, the combination of reserpine with hydrochlorothiazide (Ser-Ap-Es) was the first fixed-dose combination therapy approved for use in the United States. The historical evolution of fixed-dose combinations for treatment of hypertension is summarized in table 2.5.

Table 2.5: Historical evolution of fixed-dose combination therapy (Epstein & Bakris, 1994:1970)

1960s
Reserpine-hydralazine-hydrochlorthiazide (Ser-Ap-Es)
Methyldopa/thiazide diuretic
1970s
Thiazide/potassium-sparing diuretic
Thiazide/spirinolactone
β-Blocker/thiazide diuretic
Clonidine/thiazide diuretic
1980s
Angiotensin-converting enzyme inhibitor/thiazide diuretic
1990s
Low-dose β-blocker/thiazide diuretic
Angiotensin-converting enzyme inhibitor/calcium antagonist

2.3.2 How to use combination therapy

According to Moser and Black (1998:77S) there are several ways to use combination therapy:

- Each individual component can be titrated and once the appropriate dosage of each is reached, a fixed-dose combination that contains the approximate doses of each component can then be given.
- Start therapy with a single agent (drug 1) and then use a fixed-dose combination that includes a second agent and the dose of drug 1 as the next step.

- Start the patient on a fixed-dose combination with small doses of two different classes of drugs. This approach may achieve good blood pressure control more quickly with minimal side-effects.

2.3.3 Advantages of combination therapy and fixed-dose combinations

According to Moser and Black (1998:76S), combination therapy presents many advantages compared to using large doses of a single agent, and in some situations fixed-dose combinations have advantages over using each drug separately. The efficacy of the combination of two medications in lower doses is usually greater than blood pressure lowering effects of either agent in higher doses. These potential advantages include:

- Better tolerability
- Favourable alteration in pharmacokinetics
- Greater efficacy
- Improved compliance
- Possible lower cost

Some of these advantages will be discussed more in detail below:

- **Improved patience compliance**

The stepped care approach to the treatment of hypertension suggests starting at a low dose of a single antihypertensive agent and titrating up to the highest recommended dose. This approach may contribute to poor compliance rates. Because most adverse events are dose dependent, the likelihood of side-effects in patients is higher. Thus, the perception of many physicians that fewer side-effects occur with monotherapy is wrong. In addition to this, most of the low-dose combination drugs available include components which have 24 hour efficacy and thus are also true once-a-day agents (Neutel *et al.*, 2001:287). Having to take fever tablets should lessen the chance that the patient might confuse medications and should reduce the number of treatment failures that might result from missed doses (Epstein & Bakris, 1996:1972).

Another factor that influences patient compliance is complicated treatment regimens with polypharmacy. There are now multiple low-dose combination agents available that can be dosed as one tablet/capsule once daily. The use of such agents will simplify treatment regimens, which may result in improved compliance rates (Neutel *et al.*, 2001:288).

- **Cost of combination drugs**

Despite the common belief that combination therapy is more expensive than monotherapy, this is not true in many instances. Low-dose combination agents are usually marketed as a "package deal" in that they are more expensive than each of its components but cheaper than when each of the components is used separately in the same patient (Neutel *et al.*, 2001:290). Furthermore, many patients are limited to a certain number of drugs by their medical plan, if they exceed this number they are responsible for paying for their drugs. The use of a combination agent represents only one drug and allows another drug to be covered by their plan, which may result in a decreased pharmacy cost for the patient (Neutel *et al.*, 2001:291).

2.3.4 Disadvantages of combination therapy

Moser and Black (1998:77S) stated that there are however some disadvantages of using fixed-dose combination therapy:

- Dose flexibility may be lost
- Fixed-dose combinations may not have the appropriate doses for one or both of the drugs needed to threat some co-morbid conditions.

In treating heart failure, for example, where larger doses of ACE inhibitors are often necessary, fixed-dose combination might require giving excessively high doses of the other component than would be appropriate for those patients (Moser & Black, 1998:77S).

2.3.5 Therapeutic strategies for using combination therapy

In most, if not all, hypertensive patients, therapy should be started gradually, and the target blood pressure values should be achieved within several weeks. To reach such target values, it is likely that a large proportion of patients will require combination therapy with one or more agent. The proportion of patients requiring combination therapy will depend on baseline blood pressure values. According to baseline blood pressure and the presence or absence of complications, it appears reasonable to initiate therapy either with a low dose of a single agent or with a low dose combination of two agents (European Society of Hypertension, 2003:1032) (refer to Figure 2.12).

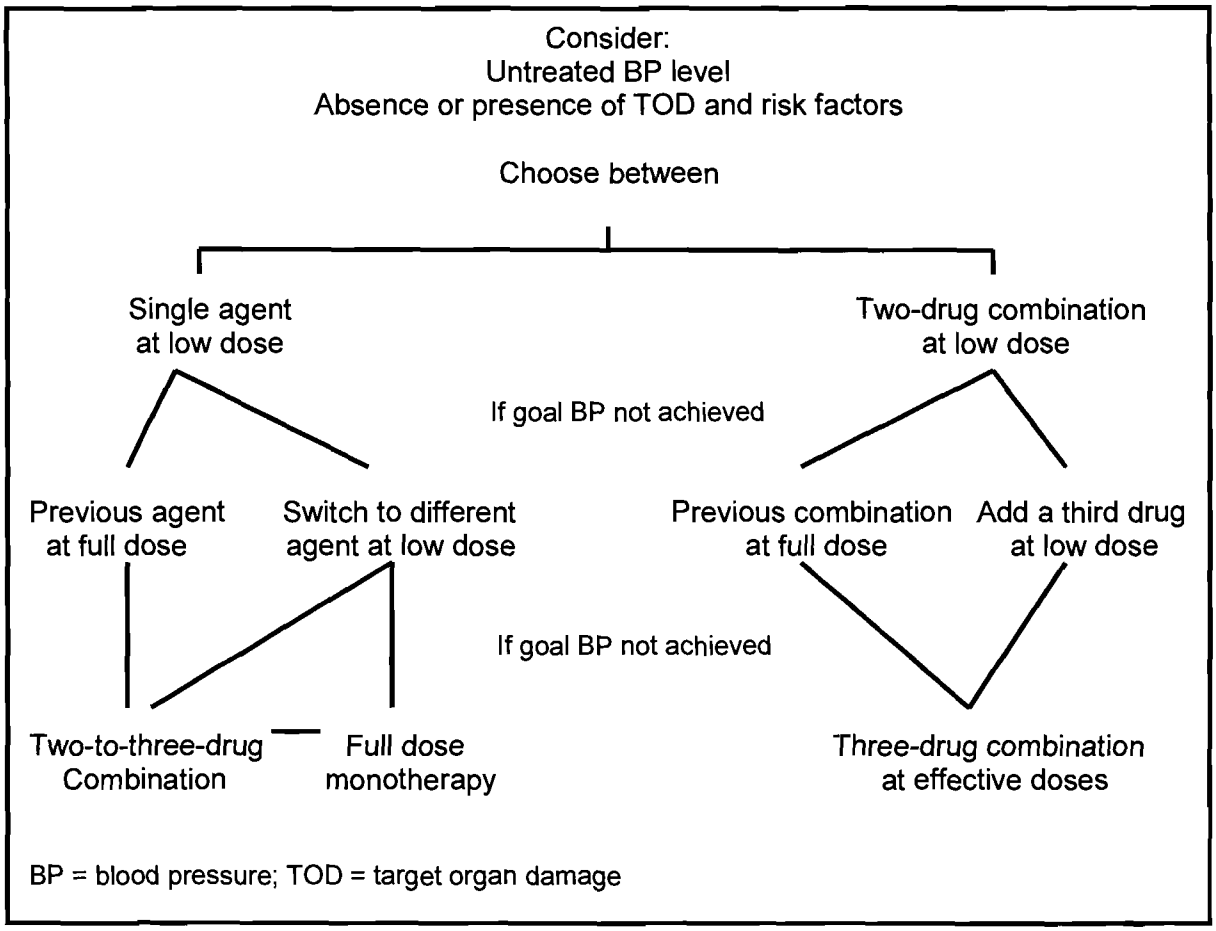


Figure 2.12: Choice between monotherapy and combination therapy (European Society of Hypertension, 2003:1033).

If low-dose monotherapy is chosen and blood pressure control is not achieved, the next step is to switch to a low dose of a different agent, or to increase the dose of the first compound chosen (with a greater possibility of causing adverse effects) or to move to combination therapy. If therapy has been initiated by a low-dose combination, a higher dose combination can subsequently be used or a low dose of a third compound can be added.

The advantage of starting with low dose monotherapy and, if the initial compound is not well tolerated, switching to another agent, is being able to find the drug to which any individual patient best responds (both in terms of efficacy and tolerability). But, unless pharmcogenomics provides help in the future, the procedure is extremely laborious both for doctors and patients, and this leads to low compliance (European Society of Hypertension, 2003:1032).

An obvious disadvantage of initiating with two drugs, even if at a low dose, is that of potentially exposing the patient to an unnecessary agent, but the advantages are:

- By using two drugs with different mechanisms of action, it is more likely that blood pressure and its complications will be controlled.

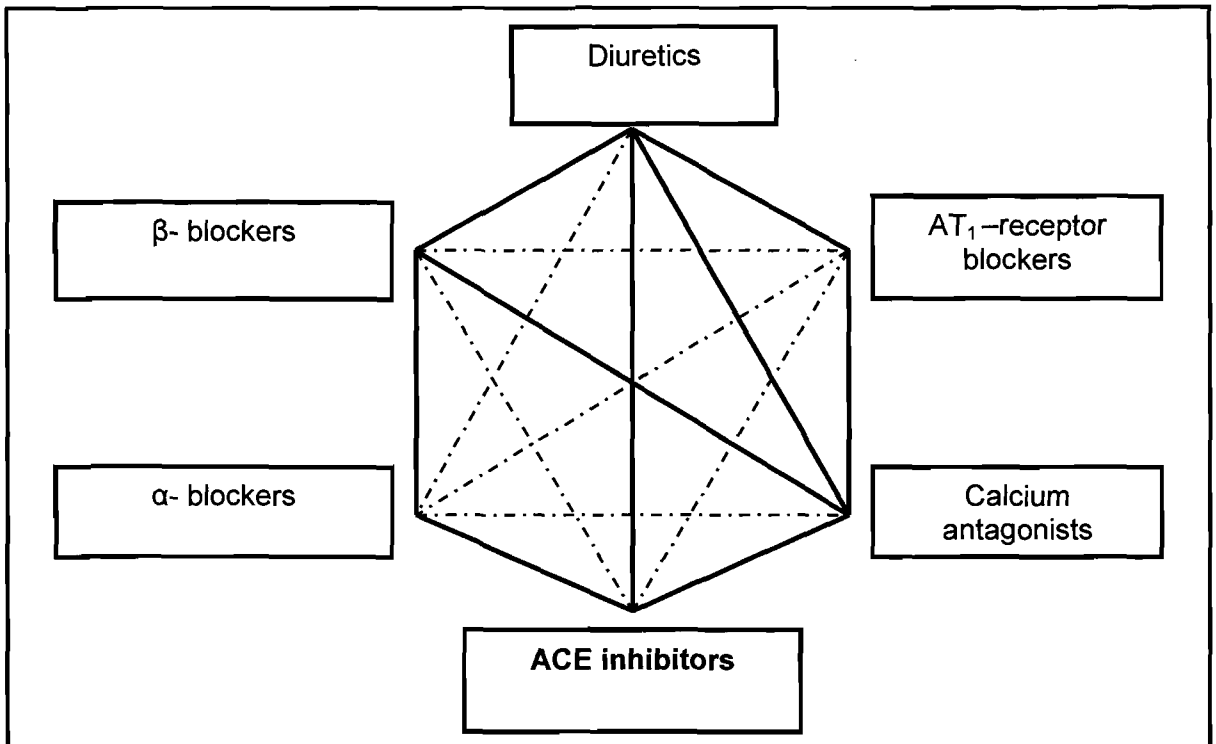
- By using combinations, both the first and second drugs can be given in the low dose range that is more likely to be free of side-effects.
- Allowing the administration of two agents with a single tablet, thus optimising compliance.

2.3.6 Two-drug combinations

This can be another way to present the combination medicine.

According to the European Society of Hypertension (2003:1033-1034) the following two-drug combinations have been found to be effective and well tolerated (refer to figure 2.13 below):

- Diuretic and β- blocker
- Diuretic and ACE inhibitor
- Calcium antagonist (dihydropyridine) and β- blocker
- Calcium antagonist and ACE inhibitor or angiotensin- receptor antagonist
- Calcium antagonist and diuretic
- α- blocker and β-blocker
- Other combinations (e.g. with central agents, including α_2-adrenoreceptor antagonists and imidazoline I_2 receptor modulators, or between ACE inhibitors and angiotensin receptor antagonists) can be used if necessary, and three to four drugs may be required in many cases.



The most rational combinations are represented as thick lines. The frames indicate classes of antihypertensive agents proven to be beneficial in controlled interventional trails.
ACE = angiotensin-converting enzyme.
AT_1 = angiotensin receptor $_1$

Figure 2.13: Possible combinations of different classes of antihypertensive agents (European Society of Hypertension, 2003:1033).

2.3.6.1 Benefits of combining an ACE inhibitor and Calcium-channel blockers (CCB)

These two drug classes work in entirely different ways, both providing peripheral vasodilatation with little direct effect on cardiac output (Kaplan, 2001:9S). Perhaps the most beneficial effects of the ACE inhibitor-CCB combination have been found in patients with renal insufficiency, in particular related to diabetic nephropathy (Kaplan, 2001:9S). ACE inhibitors protect against progressive renal damage and reduce proteinuria by their preferential effect on efferent antriolar resistance, reducing intraglomerular pressure. The CCB will preserve renal perfusion and glomerular filtration. This combination is recognized as an effective therapy for reducing both systemic and intrarenal hypertension, thereby protecting the kidneys (Kaplan, 2001:9S). Combinations of ACE inhibitors and calcium antagonists have fewer side-effects than either agent alone. As an example, there are reports of significantly reductions in the incidence of pedal oedema induced by dihydropyridine calcium antagonists when ACE inhibitors are added. This reduction is largely due to the venodilating capacity of the ACE inhibitors. In addition, there have been reductions in calcium antagonist-associated constipation and headache, since the

doses of these agents are reduced when they are used in combination with ACE inhibitors (Epstein & Bakris, 1996:1974). It can therefore be concluded that the combined use of a calcium antagonist and an ACE inhibitor offers a useful means by which elevated blood pressure can be lowered. Relative to other therapies, this is still an expensive combination (Hansson & Himmelmann, 1994:1145).

2.3.6.2 Benefits of combining ACE inhibitors and Angiotensin-receptor blockers (ARB)

The major use of ARBs in addition to or in substitution of ACE inhibitors may be appreciated through the understanding of the ACE *escape concept,* which is a decrease in the efficacy of ACE inhibitors secondary to an increase in circulating angiotensin-II levels from chronic ACE inhibition. To overcome this excess angiotensin-II concentration, ARBs, which competitively block angiotensin-II receptor binding, may be used. Although angiotensin-II receptor upregulation may occur, experimental data suggests that there is insufficient angiotensin-II to overwhelm the ARB drug concentration at the receptor site to achieve full receptor occupancy, which suggests that ACE inhibitors and ARBs may have an additive effect (Wong *et al.*, 2004:126).

2.3.6.3 Benefits of combining ACE inhibitors and diuretics

The combination of an angiotensin-converting enzyme inhibitor and a thiazide diuretic is usually markedly effective in lowering elevated arterial blood pressure (Hansson & Himmelmann, 1994:1144). The activation of the renin-angiotensin system induced by diuretic treatment contributes to the marked efficacy seen when an ACE inhibitor is added to the therapeutic regimen. In a multicentre trial comprising 286 patients with mild to moderate hypertension, the superior efficacy of low-dose lisinopril plus hydrochlorothiazide to the effect of the monocomponents was clearly shown. Similarly, in another multicentre trial comprising 108 patients, hydrochlorothiazide was added to perindopril or captopril, and again a high proportion of normalized blood pressure was observed in the patients receiving combined therapy. It can be concluded that the combined use of an ACE inhibitor and a diuretic offers a useful, effective and well tolerated therapeutic regimen for elevated arterial pressure (Hansson & Himmelmann, 1994:1144).

2.3.6.4 Benefits of combining ACE inhibitors and β-blockers

There is no obvious pharmacological rationale for the combination of a β-blocker and an ACE inhibitor, since both classes of compounds have an inhibitory effect on the renin-angiotensin-aldosterone system, work by different mechanisms, and since the vasodilating effect of the ACE inhibitors is obtained without incurring reflex tachycardia, thereby obviating the need for β-blockade (Hansson & Himmelmann, 1994:1146). In an early study, using propranolol in a dosage of 600mg/day, the addition of either a diuretic or β-blocker produced a further fall in blood pressure, and there was no significant difference in the effectiveness of the two additions regarding their effect on blood pressure. In a large clinical trial comprising of some 300 patients the combined use of lisinopril and atenolol was evaluated, and again the clinical usefulness of combined treatment was doubtful. An interesting observation was that patients younger than 50 years of age had a more marked fall in blood pressure than patients over the age of 50 years. It can be concluded that using a β-blocker and a converting enzyme inhibitor together in the treatment of hypertension appears to be a less than optimal combination, and there is no rationale for combining the two (Hansson & Himmelmann, 1994:1146).

Combination therapy with ACE should be considered because the evidence promoting its use and the advantages of using these combinations surely outweigh the disadvantages and will ultimately lead to better compliance and containment of cost.

2.4 Generic substitution

Mott and Cline (2002:663) mentioned that spending for prescription drugs has been one of the fastest growing components of health care expenditures since 1990. The annual percentage increase in prescription drug expenditures averaged 12.2% between 1990 and 1999. Slowing the rate of growth in prescription drug expenditures could be accomplished by increasing the use of generic drugs because of the large cost difference between brand and generic drugs.

With prescription drugs becoming more expensive, it may be a good idea to consider generic drugs. Although generic drugs have been available for many years, many people are not fully aware of what they have to offer. Generic drugs can provide a less expensive way for people to obtain the medication they need (The Association of the British Pharmaceutical Industry, 1999?).

2.4.1 What is a generic medicine?

Generic medicines are the equivalent of the brand-name medicines. They contain the exact same active ingredient, strength and dosage form as the original product (Mestern, 2003).

2.4.2 What is generic prescribing?

Generic prescribing is when a doctor prescribes a medicine using the generic name of its active ingredient. The name given to a medicine when it is first licensed for use is its trade name, or brand or property name, and this identifies it as the exclusive property of the particular company (The Association of the British Pharmaceutical Industry, 1999?).

2.4.3 What is generic substitution?

Generic substitution is different to generic prescribing in that the doctor's choice to write a prescription with a generic or a brand name can be overwritten by the pharmacist, without consulting either the doctor or pharmacist. This means that the pharmacist has the freedom to dispense any generic version of the product instead of the brand name written on the prescription by the doctor (The Association of the British Pharmaceutical Industry, 1999?).

2.4.4 Why are generic drugs less expensive?

Generic drugs are usually less expensive because generic manufacturers do not have the investment costs of the developer of a new drug, and new drugs are developed under patent protection (Center for Drug Evaluation and Research, 2004). The patent gives the manufacturer exclusive rights to market the product to the public for a certain length of time. When the patent expires, other pharmaceutical manufacturers may reproduce the same medicine under a different name. The generic medicine is less expensive, since it did not have to undergo the same expensive research and development (Global Health Medical Scheme, 2007).

2.4.5 Legislation and generics

According to Mestern (2003) the new legislation regarding generic substitution in South Africa, came into effect on 2 May 2003. The National Drug Policy for South Africa (1996:10) added that the responsibility of the pharmacist is to inform the patient on the benefits of generic substitution, prior to dispensing the prescription as well as to ensure that the substitution takes

place with the patient's full understanding and consent. In accordance with the new generic medicine legislation, the following apply:

- If the person prescribing the medicine has written in his or her own handwriting on the prescription the word "no substitution" next to the item prescribed, then the prescribed item should not be substituted (SA, 2003:MAE30)
- The patient has the right to refuse the substitution to the generic medicine, then the innovator item should be provided (Mestern, 2003)
- If the retail price of the interchangeable multi-source medicine is higher than that of the prescribed medicine, then the patient should choose whether he/she prefers the innovator or the generic (SA, 2003:MAE30)
- Where the product has been declared not substitutable by the council, then the item prescribed should be dispensed (SA, 2003:MAE30).

The National Drug Policy for South Africa (1996) will aim at achieving generic prescribing in both the public and private sectors. Until this aim is achieved, generic substitution will be allowed, through legislation, in the public and private sector. Mestern (2003) further mentioned that it is no longer necessary to consult with the doctor prior to making a generic substitution. The decision to substitute now rests with the patient, following the advice of the pharmacist. The National Drug Policy for South Africa (1996:10) therefore stated that patients have the right to make informed decisions concerning their own health, including a choice for generic drugs.

2.4.6 Model for generic drug use

To examine the opportunity for generic drug use and generic substitution a more complete conceptual model for generic drug use can be used (Figure 2.14).

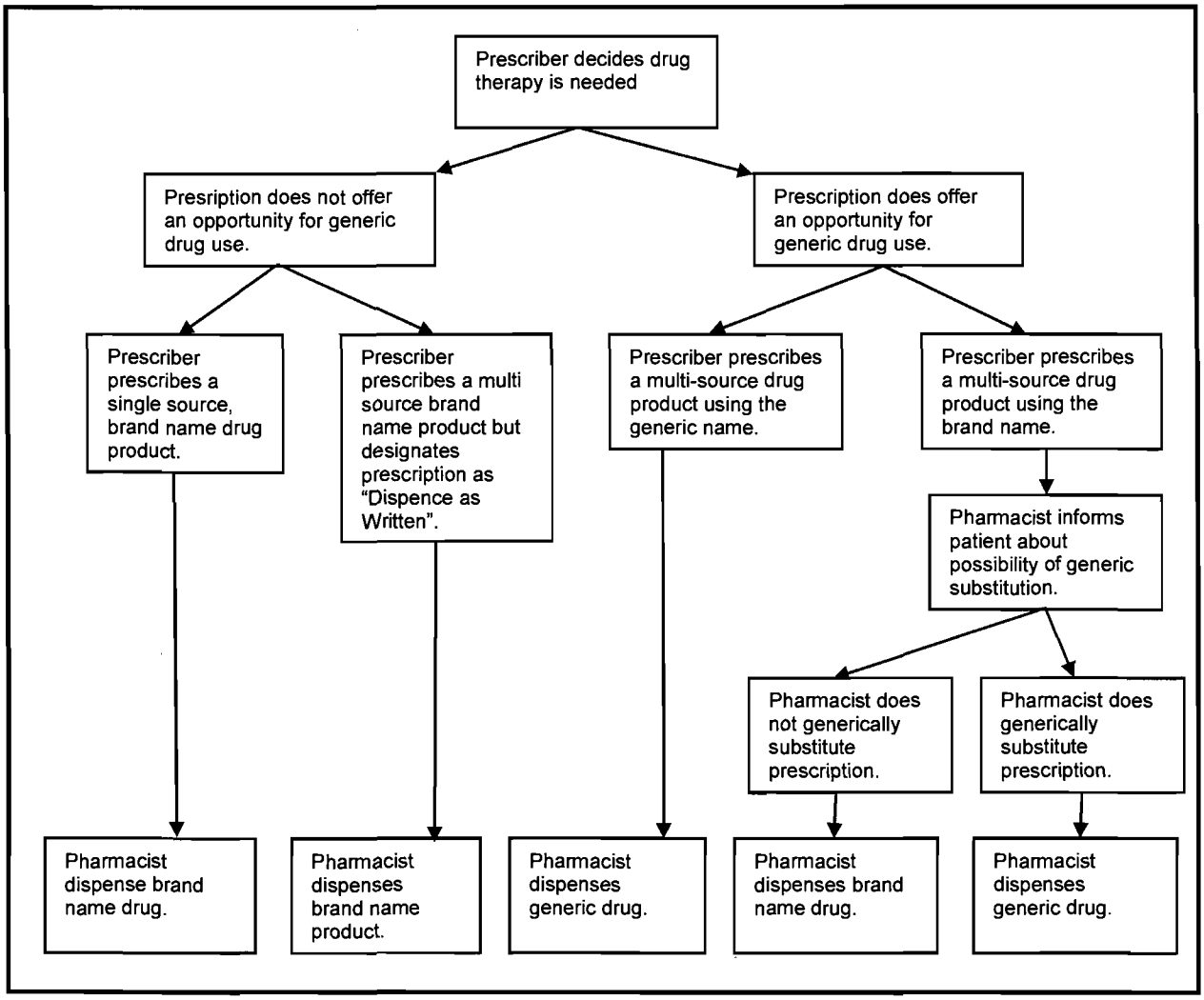


Figure 2.14: Conceptual model for generic drug use (Mott & Cline, 2002:664).

The opportunity for generic drug use exists when the prescription is written using the generic drug name of a multisource drug. In the first case, a generic drug is dispensed and used by the patient. In the second case, a generic drug is dispensed and used by the patient depending on decisions made by both the patient and pharmacist (and in some cases the prescriber) to generically substitute the prescription. When the opportunity for generic drug use does not exist (either because a single-source drug is prescribed or a prescriber designates a prescription as "dispense as written"), a brand name drug is dispensed and used by the patient. Factors such as prescriber and pharmacist characteristics and drug characteristics may be associated with the opportunity for generic drug use and generic substitution (Mott & Cline, 2002:663).

Patient variables and characteristics of drugs also may be associated with generic drug use. Although increasing age is associated with less favourable attitudes towards generic drug use, patients older than 65 years are less likely to have prescription drug insurance relative to

younger patients, thus possibly increasing the use of generic drugs to save money. Furthermore, drugs prescribed to treat chronic disease conditions are less likely to be generically substituted, possibly because consumers are less likely to use generic drugs when treating chronic conditions. The longer a generic version has been available, the more experience physicians and pharmacists likely are to gain with the generic version, thus promoting its use (Mott & Cline, 2002:664).

2.4.7 Problems regarding generic substitution

The following possible problems with regard to generic substitution include:

- The main problem would be that the doctor's judgment does not prevail about the individual patient. Doctors freely prescribe generics in cases where they feel that the generic has no disadvantages compared to the brand name product (The Association of the British Pharmaceutical Industry, 1999?).
- While the generic product should have the same key clinical characteristics as the branded product, it is often packaged differently, has a different shape and/or colour. This can create problems, especially with older patients who have to take a variety of medications at different times of the day, and this could lead to confusion for the patients, and thus to failure to adhere to treatment (The Association of the British Pharmaceutical Industry, 1999?).

2.4.8 Limits of generic prescribing

According to The Association of the British Pharmaceutical Industry (1999?) it is not unusual for doctors to prefer to prescribe the innovator items even when a generic is available, because they are concerned that a change of medication could influence compliance with the course of treatment. Patients with certain conditions or particular sensitivities should not deviate from their regular medication, so for safety reasons, there is a limit to the degree to which generic prescribing can take place. Despite the concerns, some commentators have recommended a policy that would prevent doctors from ensuring that their patients get the medicines they specify on their prescriptions. This policy is called generic substitution (The Association of the British Pharmaceutical Industry, 1999?).

2.5 Chapter summary

When first introduced in 1981, angiotensin-converting enzyme (ACE) inhibitors were indicated only for the treatment of refractory hypertension. Since then, they have been shown to reduce morbidity and mortality in congestive heart failure, myocardial infarction, diabetes mellitus, chronic renal insufficiency, and atherosclerotic cardiovascular disease (Bicket, 2002:461).

It is clear that ACE inhibitors represent one of the major advances in cardiovascular therapeutics over the past 20 years. It is highly doubtful that even the most enthusiastic advocate of these agents could have anticipated their broad clinical applications (Brown *et al.* 1998:1416).

Chapter 3 will contain an overview of pharmacoeconomics, drug utilisation review as well as managed care and the chapter will conclude with aspects of pricing regulations.

Chapter 3

An overview of pharmacoeconomics, drug utilisation review and managed care

The previous chapter focussed on the nature of ACE inhibitors, cardiovascular medicine, diseases and reasons for using ACE inhibitors as first-line antihypertensive therapy. The chapter concluded with elements of generic prescribing and combination therapy (with regard to ACE inhibitors).

This chapter contains an overview of the important aspects of pharmacoeconomics (with reference to practical applications of ACE inhibitors) and drug utilisation review. The basic elements of managed care will be discussed briefly, as well as the relation between pharmacoeconomics, drug utilisation review and managed care respectively. This chapter concludes with aspects of the pricing regulations, implemented by the Department of Health during 2004.

Economic evaluation of treatment innovations in medicine is seen as increasingly important in most societies because the resources granted to healthcare are limited (McMurray *et al.*, 1997:1414).

The cost of medical care in general, and of pharmaceutical products specifically is, being felt in nearly all developed, as well as developing countries. South Africa is no exception. During recent years, increasing emphasis has been placed on the cost of medicine and factors influencing it. This is also evident from the new National Drug Policy for South Africa, where one of the economic objectives is *"to promote the cost-effective and rational use of drugs*" (Truter, 1997:19).

Drug costs *per se* are important, as they account for a substantial part of the total cost of health care: typically 10-15% in developed countries and up to 30-40% in some developing countries (WHO, 2003b). However, drug costs usually need to be interpreted in the context of the overall (net) costs to the health system. Drugs cost money to buy, but the use of drugs may also save costs in other areas (WHO, 2003b).

3.1 Pharmacoeconomics

3.1.1 Introduction

According to Szucs (1997:272S-273S) the study of pharmacoeconomics has experienced an extraordinary boom within the health care sector over the years, as a wide range of techniques have been developed to evaluate the economic impacts of clinical care and medical technology. Health economists start with the basic premise that, whereas desires and needs are infinite, resources are limited. Therefore, health economists try to find the best way to allocate these resources appropriately in order to maximize the overall health of the population, with the search for increased effectiveness (the impact of an intervention on outcomes) and efficacy (whether an intervention is capable of favourably affecting outcomes) of health care services and products as the common factor (see figure 3.1).

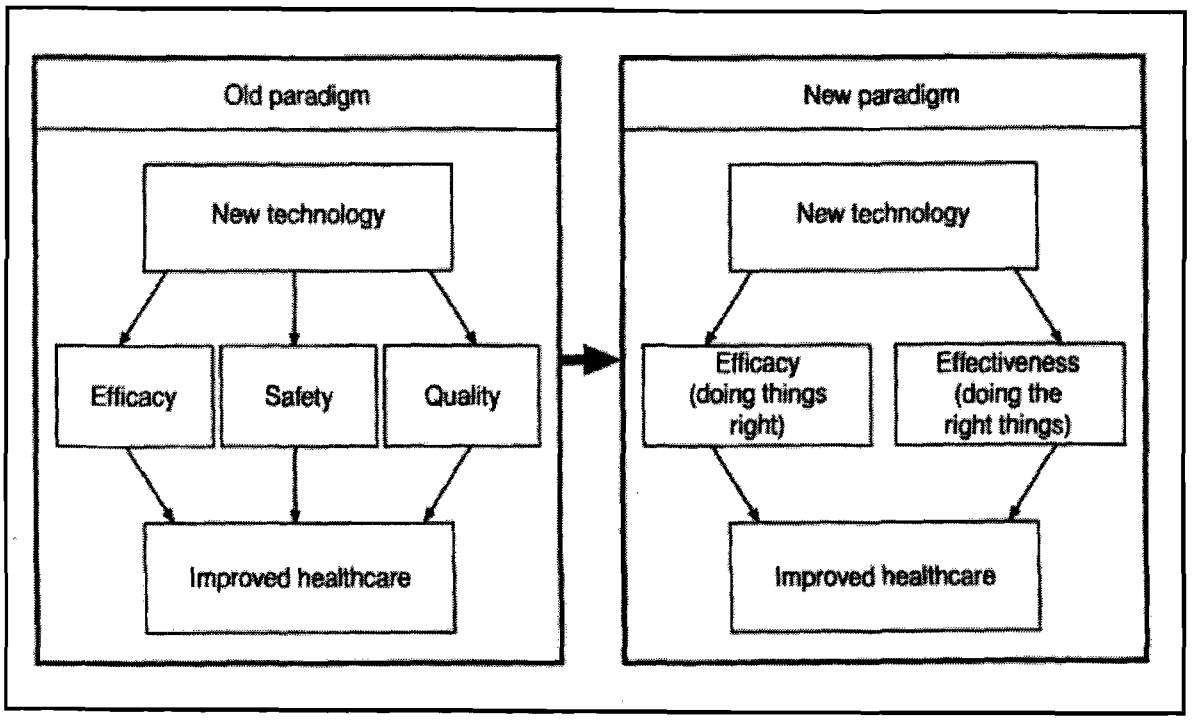


Figure 3.1: Comparison of the old and new paradigms; future technologies will have to meet the new challenges of efficacy and effectiveness (Szucs, 1997:273S)

Health economics and pharmacoeconomics employ tools to identify, measure, and compare the costs and consequences of medical interventions, including drug therapy. Economic evaluations of health care alternatives are becoming increasingly common as managed care organisations, hospitals, governments, other providers, and payers seek the optimal use of limited health care resources (Struwig, 1997:2).

Economic assessment of health care developed in response to the needs of administrators, third party payers, and politicians, who needed to understand the consequences of technological changes in health care. However, decisions relating to the use of technologies used to be based entirely on the clinical efficacy, safety, and quality of the products used. Increasing medical costs, as well as unique burdens associated with managing chronic diseases, have sensitized health care decision-makers in both the public and private sectors to the problems of scarcity of resources and competing interventions. Now, the economic impacts of a product require assessment before such product it is widely indorsed (Szucs, 1997:173S).

3.1.2 Definition

Pharmacoeconomics can be defined as *"the description and analysis of the costs of drug therapy to healthcare systems and society".* (Bootman *et al.*, 1991:4). Cantor (2002:S29) however defined pharmacoeconomics as the identification, measurement, and comparison of pharmaceutical products and services based on clinical benefits and economic costs. Furthermore, Cantor (2002:S29) stated that pharmacoeconomics is an interdisciplinary science that incorporates elements from pharmacy, clinical medicine, clinical epidemiology, statistics, psychology, economics, and ethics.

In essence, pharmacoeconomic analysis employs important tools for examining the impact of drug therapy and related medical interventions (Bootman *et al.*, 1996:7).

3.1.3 Benefits of pharmacoeconomics

Health economics evaluations can bring benefits to various interested parties, such as (Szucs, 1997:274S):

- **Third party payers**

Third party payers are able to formulate better policies and reach more informed decisions when allocating funds or negotiating contracts with health care providers. In addition, a better mix of health care services offered to the insured population can be coordinated. One of the most important advantages of pharmacoeconomics for third party payers, however, is the ability to make more informed management decisions, through a more transparent cost structure and better forecasting of demographic and epidemiologic shifts and their subsequent impact.

- **Health care providers**

Providers benefit from pharmacoeconomics by optimizing their mix of clinical strategies and their ability to choose from alternative services.

- **Manufacturers**

Manufacturers benefit in two ways: proactively and reactively. Proactively, the industry can establish the *true value* and appropriateness of its products. Reactively, manufacturers can meet the demands of health care administrators, providers, and politicians for economic data. In a competitive world, all manufacturers will need to carry out such evaluations to meet the demands of their customers.

- **Patients**

Patients will have to bear more and more of the health care bill, either through co-payments or by risk-adjusted insurance premiums. Therefore, their choices will be based on the *perceived value* of services or products offered. In these instances, value does not simply mean the actual cost of a service or product, but it also includes patient preferences for different types of testing and treatments in addition to their expectations of health outcome. As a result, analyses of patient preferences, which include quality of life assessments, are a growing part of health economic research.

Most substantial benefits offered by pharmacoeconomics can be realised in pharmacy practice environments including hospitals and managed health care organisations (Sanchez, 1996:291-292). Some of these benefits are the following:

- Pharmacoeconomic analysis can be used to assess the value of pharmaceutical products and services.
- Pharmacoeconomics can provide data necessary to make better drug use decisions.
- Pharmacoeconomic data allow pharmacists to balance cost with quality and patient outcome.

3.1.4 Steps in pharmacoeconomic research

There are several steps in performing and designing a pharmacoeconomic study that should be addressed (Bootman *et al.*, 1991:13). These steps are illustrated below (Bonk, 1999:88):

Step 1: Define the study objective and research perspective. What specifically does the study achieve to determine?

Of the four main types of pharmacoeconomic studies the one that is applicable to this study is cost-minimization due to generic substitution (also refer to section 3.1.6.1). This

study also determines the prescribing patterns of angiotensin-converting enzyme inhibitors.

Step 2: Identify any alternative agents and their methods of comparison. Does the study involve a comparison of all relevant alternatives for treatment?

This study also involves a comparison of ACE inhibitor innovator items and generic items.

Step 3: Measure outcomes as appropriate to the analysis type. What are the main outcome measurements in this therapeutic situation?

With regard to this study the main outcomes will be measured and assumed to be equivalent in comparative groups (i.e. innovator items *versus* generic items) (refer to section 3.1.7.1).

Step 4: Value cost categories appropriate to the perspective. Which cost categories should be included in this study? Are inflation, discounting, and other related issues addressed in these calculations?

Step 5: Calculate summations and ratios of costs versus outcomes. Were costs and outcomes meaningfully summed?

Step 6: Conduct sensitivity analysis of research assumptions. Which assumptions or calculations inherently introduce uncertainty into the research?

Step 7: Interpret and disseminate the findings of the research study. What do these findings mean in the context of study objectives and research perspectives.

3.1.5 Cost-analysis

The concept of cost deals with the resources that are used in the production of a product or service (Larson, 1996:45). Struwig (1997:169) however stated that most economists would define cost as the consumption of a resource that otherwise could have been used for another purpose (opportunity cost). Costs are the actual amount of resources consumed to attain a certain benefit. Different costs must be taken into account:

3.1.5.1 Direct cost

Direct costs are usually represented by the sum of expenditure involved in the consumption of medical and non-medical products or services. Direct costs usually include hospital costs, physician fees, cost of drugs, laboratory tests, rehabilitation, and therapies. Non-medical direct

costs are expenses generated by the patient or his family that are directly related to treatment such as food, accommodation and travel expenses (Struwig, 1997:169).

With regard to this study only direct costs are applicable such as cost of the drugs.

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3.1.5.2 Cost-of-illness and cost-of-therapy

An illness consumes resources and thus, it has a cost. The cost of an illness is the sum of three components (Larson, 1996:47):

- The medical resources used to treat the illness, which includes hospital care, professional services, drugs, and supplies.
- Non-medical resources associated with it. These include transportation to the site of treatment, lodging of family during treatment, and the hiring of a person to help with home care.
- Loss of productivity due to illness or disability (indirect costs).

The cost of therapy, on the other hand can be classified as medical, direct non-medical and indirect. For example, medical cost includes (Struwig, 2001:60-61):

- Hospital care
- Personnel
- Drugs
- Supplies

Direct non-medical cost includes:

- Transportation
- Lodging

Indirect costs include loss of productivity.

With regard to this study hospital care, personnel, supplies and non-medical costs are not applicable to the results.

Struwig (2001:61) also added that in addition, therapy can also cause other resources to be consumed, and must be considered as part of the total cost of therapy. An example includes the use of resources in the treatment of adverse effects.

3.1.6 Overview of pharmacoeconomic methodologies

Pharmacoeconomic evaluations include any study designed to assess the costs and consequences of alternative therapies. This includes methodologies such as cost-benefit, cost-utility, and cost-effectiveness (Bootman *et al.*, 1991:5).

These are summarised in Table 3.1, and will be discussed in more detail later in the chapter.

Table 3.1: Pharmacoeconomic Methodologies (Adapted from Bootman *et al.*, 1996:9)

METHODOLOGY	COST MEASUREMENT UNIT	OUTCOME UNIT
Cost-benefit	Monetary (rand value)	Monetary
Cost-effectiveness	Monetary (rand value)	Natural units (life-years gained, mg/dL, blood sugar, mm Hg blood pressure)
Cost-minimization	Monetary (rand value)	Assumed to be equivalent in comparative groups
Cost-Utility	Monetary (rand value)	Quality-adjusted life-year or other utilities

3.1.6.1 Cost-minimization analysis (CMA)

When two or more interventions are examined and demonstrated or assumed to be equivalent in terms of a given outcome or consequence, costs associated with each intervention may be examined and compared. This typical cost-analysis is referred to as cost-minimization (CMA) analysis (Bootman *et al.*, 1996:10).

CMA could appropriately be used to compare a branded drug with a generic equivalent (also refer to chapter 2, section 2.4 for generic substitution of medicine items). As the clinical outcomes associated with the two therapies are assumed to be equivalent, costs can be compared. CMA could also be used to compare agents in the same therapeutic class that have been shown to be equivalent in safety and efficacy. Thus CMA may be used to justify generic or therapeutic substitution (Struwig, 1997:100). In this study generic items over different periods will be compared.

According to the WHO (2003b), if a new therapy is not 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. An example would be the introduction of a new ACE inhibitor with essentially the same properties as existing members of the class; the price would be equivalent to that of the existing drug(s). This is often not as simple as it may seem, as it requires sound-based information on the doses of the two drugs required for equivalent efficacy.

3.1.6.2 Cost-benefit analysis

Cost benefit analysis (CBA) is not a new concept used in evaluating health interventions. Basically, CBA is a tool that can be used to improve the decision making process in allocation of funds to healthcare and other programmes (Bootman *et al.*, 1991:5).

Cost-benefit analysis (CBA) is a method for comparing the value of all resources consumed (costs) in providing a programme or intervention against the value of the outcome (benefits) from that programme or intervention. CBA is a tool that can be used to guide the decision-making process in the allocation of funds for health and other programmes. Cost-benefit analysis requires that the costs and benefits both be valued in the same units, usually dollars (McGhan & Kitz, 1996:61).

One advantage is that it enables comparisons to be made between health care programmes with different outcomes and to take into account all the possible outcomes of the interventions (each being translated into monetary terms). The primary disadvantage of CBA is the difficulty of estimating the monetary value that patients would place on outcomes e.g. number of cures, years of life saved, decrease in blood glucose. For this reason CBA is not typically used to evaluate therapeutic alternatives in the managed health care setting. CBA is more commonly used to demonstrate the value of pharmaceutical services for resource allocation decisions in a hospital or in public policy setting (Struwig, 1997:126). Cost-benefit analysis is therefore not a direct part of this study because alternatives are evaluated.

3.1.6.3 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a technique designed to assist a decision-maker in identifying a preferred choice among possible alternatives. Cost-effectiveness is defined as a series of analytical and mathematical procedures that help in the selection of a course of action from various alternative approaches (Bootman *et al.*, 1996:11). In this form of economic evaluation, the consequences of each intervention (pharmacological and non-pharmacological) are measured in the most appropriate natural physical unit, such as "years-of-life gained", while

the costs are measured in monetary terms. No attempts are therefore made to attach a "value" to the consequence (Struwig, 1997:85).

With respect to drug therapy, these alternative interventions may be two or more different drugs or classes of drugs. The goal may be to compare drug treatment with one or more types of non-drug treatment for a particular condition (Chrischilles, 1996:77).

Cost-effectiveness is used to imply value for money. If one drug costs less and is more effective than another, it is clearly the more cost-effective of the two. However, when drug costs are more and the drug is more effective than another, the decision of relative cost-effectiveness depends on whether the decision-maker believes the extra effectiveness is worth the cost (Chrischilles, 1996:99).

The main advantage of cost-effectiveness analysis is that it considers the possibility of improved outcomes in exchange for the use of more resources (Struwig, 1997:118).

This methodology will not be a direct part of this study because the outcome units will not be measured in natural units.

Examples

- **ACE inhibitors in Post-Myocardial Infarction**

The aim of this study was to assess the cost-effectiveness of three different treatment strategies for the use of ACE inhibitors after myocardial infarction (McMurray *et al.*, 1997:1411). In summary this study shows that initial treatment of relatively unselected patients, after myocardial infarction, followed by long-term treatment of those at high and medium risk maximizes benefit at an acceptable cost. Overall, use of an ACE inhibitor after myocardial infarction is very cost-effective in comparison with many other treatments, especially if a low cost ACE inhibitor is used (McMurray *et al.*, 1997:1415).

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- **The cost-effectiveness of ACE inhibitors as first-line antihypertensive therapy.**

The aim of this study was to evaluate the cost-effectiveness of ACE inhibitor therapy as antihypertensive first-line therapy as compared with conventional antihypertensive therapy with β-adenorecepteor antagonists or diuretics (Nordmann *et al.*, 2003:573). The analysis shows that the gain in life expectancy and QALYs by promoting ACE inhibitors as antihypertensive first-line therapy is very small. Furthermore, the incremental cost-effectiveness ratio of ACE inhibitors as first-line antihypertensive therapy is unfavourable when compared with

conventional antihypertensive therapy as first-line therapy according to the presence of LVH and ECG (Nordmann *et al.*, 2003:580-581).

- **The cost-effectiveness of ACE inhibitors in congestive heart failure (CHF)**

Despite the fact that ACE inhibitors have been shown to improve symptoms, reduce the incidence of clinical events associated with disease worsening, and reduce hospitalisations, ACE inhibitors remain underused. Studies performed in the UK have shown that only approximately 15% to 30% of heart failure patients in general practice were being treated with ACE inhibitors (Szucs, 1997:277S-278S). In addition, ACE inhibitors have been demonstrated to be cost-effective and their cost is falling. There is therefore a true need to encourage increasing use of patients with congestive heart failure, particularly in general practice, to provide cost-effective optimal treatment in health care systems with limited financial resources (refer to figure 3.2) (Szucs, 1997:277S-278S).

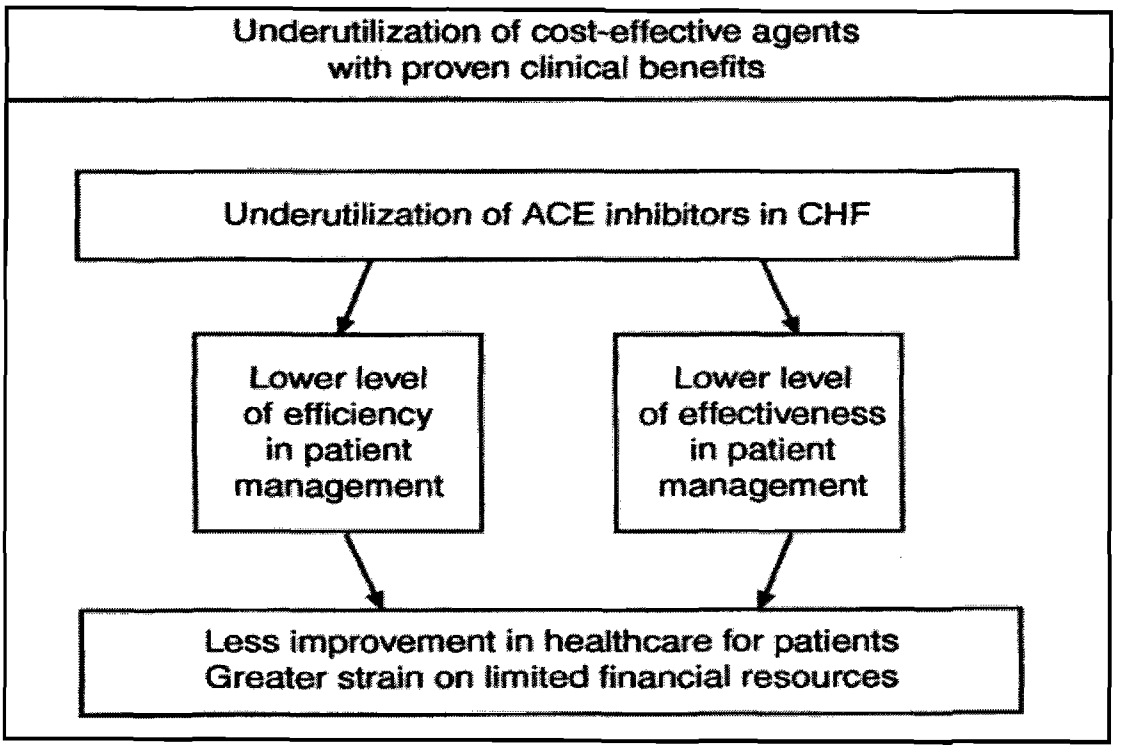

Figure 3.2: Impact of the under-use of ACE inhibitors in CHF (Szucs, 1997:227S)

3.1.6.4 Cost-utility analysis (CUA)

Coons and Kaplan (1996:104) stated that CUA is a formal economic technique for assessing the efficiency of healthcare interventions. CUA is one of the newest, and perhaps most controversial, types of economic evaluation. Some controversy stems mainly from the measurement of utility. Utility is the value or worth placed on a level of health status, as measured by the preferences of individuals or the society (Coons & Kaplan, 1996:104).

Modern medicine is concerned with the improvement of both the quality and quantity of life. For this reason, there has been a growth in interest in cost-utility analysis where life-years gained from treatment are adjusted by a series of utility weights reflecting relative values individuals place on different states of health (Struwig, 1997:127).

Due to the nature of the data of this study, it would not be possible to use this method.

Measurement of CUA

CUA is measured in monetary terms, while the units used to measure outcomes are not natural units (i.e. life-years) but units of preference or utilities. Patient preference expressed as utilities may be used to adjust the life-years offered by the therapeutic intervention. The utilities are normally derived from participant surveys that elicit patient preferences for given health states. Clinicians frequently assume that utility of death equals zero (0) and the utility of prefect health equals one (1). Quality-adjusted life-years are determined by multiplying extra years of life by quality-of-life (QOL) expressed as a utility measure (refer to table 3.2) (Struwig, 1997:127).

Table 3.2: Quality-adjusted life-years (Struwig,1997:128)

Patient lives extra two years Patient's quality of life (QOL) or utility valued at 0,5 due to health difficulties (healthy person's utility = 1,0) The Quality-adjusted life-years (QALY) = 2,0 x 0,5 = **1,0**

Uses of cost-utility analysis (Drummond *et al.*, 1997:141-142)

A cost utility-analysis can be used in the following situations:

- When quality of life is **the** important outcome. For example, in comparing alternative programmes for the treatment of arthritis, no programme is expected to have an impact on mortality, and the interest is focused on how well the different programmes improve the patient's physical function, social function and psychological well-being.

- When quality of life is **an** important outcome. For example, in evaluating cancer chemotherapy, both the survival and the quality of life being lived are important.
- When the programme affects both mortality and morbidity and a combined unit of outcome is desired.
- When the programmes being compared have a wide range of outcomes, and it is necessary to have a common unit of output for comparison. This is often the case when a decision-maker must allocate limited resources among interventions that have different objectives and resultant benefits.
- When the objective is to compare an intervention with others that have already been evaluated in terms of cost per QALY (or equivalent) gained.

By contrast CUA incorporates the quality of (or preference for) the health outcome achieved. CUA, using Quality-adjusted-life-years (QALYs) gained as the outcome measure, is the most common approach for combining quantity and quality-of-life outcomes in economic evaluations (Struwig, 1997:141).

3.1.7 Limitations of pharmacoeconomic analyses

Osterhaus and Draugalis (1991:139) mentioned that it is important to be aware of the limitations as well as the usefulness of pharmacoeconomic analysis. The questions of cost must always be followed by the inquiry "to whom?". A study conducted from different perspectives may generate different results. The question should always be asked: "Cost-effective from whose perspective?"

Pharmacoeconomics will not answer all the substantial issues. For instance, the results of a study may not be conclusive enough to improve quality of the decision-making. For example, it is important that not only drug acquisition costs are considered, as the side-effect profile of a pharmacological treatment can impact on the total costs associated with management. It is also important to be aware of the fact that health care cannot be rationed based on a simple economic calculation. There are always moral and ethical issues for society to be taken into consideration. Because pharmacoeconomic studies are expensive and time consuming, they may also increase the cost of developing and marketing a new product. Furthermore, analyses of results may be challenged, because there are no "golden standards" for conducting economic s, and many regulatory bodies do not, as yet, have the expertise to properly review and interpret economic data. Nonetheless, many countries are moving towards statutory requirements for economic evaluations of new health care products prior to their release into the marketplace (Szucs, 1997:278S).

3.1.8 Future of pharmacoeconomics

With the increasing worldwide focus on assessing relative value of new technologies and therapies, pharmacoeconomic analysis is taking on a new importance in the pharmaceutical development process (Schulman, 1996:274).

There is furthermore a vital need to produce authoritative information to assist the most important health care decisions. A strategy for health care technology assessment has four discrete, mutually reinforcing tasks and should be able to (Szucs, 1997:278S):

- Identify the technologies needing assessment.
- Collect data on the selected technology.
- Synthesize the data collected.
- Disseminate all the information collected.

One of the great challenges that society faces is that a complete system for assessment would require the monitoring of all health care technologies, both new and existing. Each technology should also be evaluated at various parts of its life cycle and the results summarised in a way that can be used by policy makers, health care providers, and the public (Szucs, 1997:278S).

3.1.9 Summary

The overall costs of medical and pharmaceutical care continue to rise. The added value to society, individual healthcare institutions and patients, as weighed against cost, has not been well established. The problem has become increasingly difficult to address because of the lack of understanding of methodologies for the evaluation of new and existing drug therapy (Bootman *et al.*, 1996:17).

The challenges of pharmacoeconomic research are exhaustible. The real challenge however is not in identifying the tools of pharmacoeconomic research, but rather in discovering how and when to use them (Bootman *et al.*, 1996:16).

3.2 Drug utilisation review (DUR)

3.2.1 Introduction

The increase of drug consumption and inappropriate drug use has led to the initiation of drug utilisation studies (Inesta, 1992:353).

Further drug utilisation research is a valuable component of quality assurance wherever medicines are used. It should thus be formally recognised and encouraged, and the necessary infrastructure for this type of research needs to be established in South Africa (Truter, 1995:338).

3.2.2 Why drug utilisation research?

The principal aim of drug utilisation research is to facilitate rational use of drugs in populations. For the individual patient rational use of drugs implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price. Without knowledge of how drugs are prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better (Sjöqvist & Birkett, 2003). Drug utilization research in itself does not necessarily provide answers, but it contributes to rational drug use in important ways as described below (WHO, 2003b).

3.2.3 Definition

Drug utilisation research is defined by the WHO as "*the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*" (Sjöqvist & Birkett, 2003).

This broad definition differs from the one which appears in North American literature, and can be defined as "the prescribing, dispensing and ingesting of drugs" (Lee & Bergman, 1994:379). This definition does not include consequences of medical, social and economic nature.

Lipton and Bird (1993:1069) defined drug utilization review (DUR) as an authorised, structured, and continuing programme that reviews, analyses, and interprets patterns of drug use against predetermined standards.

3.2.4 Classification of Drug utilisation review

According to Kreling and Mott (1993:416) drug utilisation review is used to refer to a variety of utilisation review activities. These activities can be classified into one of two categories: (a) DUR studies, and (b) DUR programme.

3.2.4.1 DUR study

A DUR study is an authorised, structured programme that reviews, analysis and interprets patterns of drug usage in a given healthcare delivery system, typically for comparison with predetermined standards (Kreling & Mott, 1993:416).

DUR studies are not interventions but rather activities aimed at problem detection and quantification. They are usually one-time projects, not routinely conducted. They provide for only minimal feedback to the involved prescribers and, most importantly, do not include any follow-up measures to ascertain whether any changes in drug therapy have occurred (Lee & Bergman, 1994:380).

- **Quantitative DUR studies**

In quantitative studies, the objective is to quantify the present state, the developmental trends, and the time course of drug usage at various levels of the health care system (Lee & Bergman, 1994:380).

A natural consequence of quantitative DUR is the development of strategies to reduce medical expenditure. Generic substitution is an example of such an action (Serfontein, 1996:6).

According to Serfontein (1996:6) quantitative DUR can be used to:

- ❖ Analyse the quantity of drugs consumed in a specific geographical area.
- ❖ Compare the consumption / prescribing of drugs in different geographical areas.
- ❖ Identify possible areas of over or under-prescribing (refer to example below).*
- ❖ Investigate the utilisation of drugs according to demographical features.
- ❖ Estimate the misuse of drugs.
- ❖ Monitor the impact of informational or regulatory activities on drug use patterns.*

* *These uses of quantitative DUR are included in this study (refer to chapter 5).*

Examples

Under-prescribing of ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been shown to be very cost effective. Too few patients are being prescribed an ACE inhibitor and, when they are, the prescribed dosage is usually lower than that shown to have beneficial effects on mortality and morbidity in the clinical trials (Andersson *et al.*, 1999:537).

The reasons for under-prescribing can be divided into patient problems, physician problems and system failure. Patient problems range from economic problems to intolerance and contraindications. A great number of reasons for under-prescribing are related to physicians and their attitudes, for instance, their concerns about potential adverse effects, mainly hypotension and cough. System failure relates to reasons external to the patient and the physician, e.g. the diagnostic facilities needed for optimal management of heart failure may not always be available (Andersson *et al.*, 1999:546-547). Masoudi *et al.* (2004:730) further mentioned that another possible explanation for the underuse of ACE inhibitors might be due to the substitution of ACE inhibitors with angiotensin-receptor antagonists (ARBs).

A study was done in America to determine ACE inhibitor use and the relationship between ACE inhibitor prescription and mortality in older patients with heart failure. It was concluded that ACE inhibitors were commonly underused in older patients with left ventricular systolic dysfunction (LVSD) without drug-specific contraindications (Masoudi *et al.*, 2004:724). These findings support existing guideline recommendations for widespread ACE inhibitor use in heart failure patients with LVSD and highlight the ongoing need for efforts to optimize the use of ACE inhibitors with the goal of ensuring that all eligible patients benefit from these life-prolonging medications (Masoudi *et al.*, 2004:730).

- **Qualitative DUR studies**

Qualitative studies assess the appropriateness of drug utilisation, usually by linking prescription data to the reasons for prescribing the drug (Lee & Bergman, 1994:380). Serfontein (1996:7) adds that this would make it difficult in the ambulatory setting because the prescription that reaches the pharmacy does not contain the diagnosis of the illness, thus making a decision on the appropriateness of the drug treatment (drug or non-drug treatment) very difficult.

Qualitative DUR utilises criteria (predetermined elements against which aspects of the quality, medical necessity and appropriateness is compared) to judge the appropriateness of the drugs used (Serfontein, 1996:7). Lee and Bergman (1994:380) further added that the crucial

difference between these studies and quantitative drug utilisation studies is that qualitative DUR studies include the concept of appropriateness.

According to Kreling and Mott (1993:417) and Sacristan and Soto (1994:300), qualitative DUR can be used to:

- ❖ Assess the appropriateness of the daily dosage (refer to chapter 5).*
- ❖ Analyse the period of time of therapy (refer to chapter 5).*
- ❖ Determine the indication of use of the specific drug or non-drug regimen.
- ❖ Identify potential drug interactions (refer to chapter 2).*
- ❖ Assess the fixed combination of drugs (refer to chapter 5).*
- ❖ Determine the most suitable dosage for each indication.

**These aspects are included in this study.*

3.2.4.2 DUR programme

A DUR programme is an intervention in the form of an authorised, structured, and ongoing system for improving the quality of drug use within a given health care institution (Lee & Bergman, 1994:380).

The goal of a DUR programme is not the collection, analysis and reporting of quantitative and qualitative information, but rather the addition to that information of corrective and educational feedback to the prescriber so that drug use can be re-evaluated and improved (Kreling & Mott, 1993:417).

3.2.5 Types of drug utilisation review

- **Retrospective studies**

A retrospective drug utilisation study is an approved, systematic process that captures, reviews, analyses, and interprets aggregate medication use data within specific health environments (Erwin, 1994:596). The data are archival of nature. Data are thus collected and analysed after the events of major interest (prescription, dispensing, and usage) have occurred (Truter, 2004:16-17). This type of review has a number of beneficial aspects (Serfontein, 1996:9):

- ❖ It can be performed quite easily using a database from a medical aid.
- ❖ 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 patient.
- ❖ It is a relatively inexpensive type of DUR method with a variety of interesting applications (This type of DUR is used in this study, refer to chapter 4, section 4.3)).

- **Concurrent reviews**

Concurrent reviews are conducted simultaneously with the dispensing process. If a potential problem is discovered, the dispensing function comes to a halt until authorization is received to continue as before or to initiate a modification or dosage correction. Concurrent reviews thus prevent therapeutic misadventures (Truter, 1994:17).

Truter (1995:338) further stated that concurrent reviews are more expensive and time consuming than retrospective studies, but have the potential for much greater pay-offs in preventing problems. A concurrent review requires a computer system or a manual drug profile system that is well organised.

- **Prospective reviews**

Prospective review is the option closest to ideal and is a more complete review than a concurrent review (Truter, 1994:18).

Chui and Rupp (2000:27) stated that prospective DUR involves the assessment of prescribed drug therapy before medication is dispensed to the patient. Pharmacists may perform a prospective review of the patient's medication regimen during the prescription screening process.

3.2.6 DUR process

Drug utilisation review is the process by which the quality of drug prescribing is measured against explicitly determined criteria or standards. Drug utilisation review is a dynamic process aimed first at rational prescribing and consequent improvement of the quality and second at minimising needless expenditures (Truter, 1994:19).

A conceptual model for using in DUR studies was proposed by Todd *et al.* (1987:530). The model is based on five essential principles required to conduct a DUR study:

- Establish authority to give DUR legitimacy.
- Determine demographic characteristics of the patient population and operational characteristics of the institution.
- Establish the current profile of drug-use patterns against which changes will be assessed.
- Review drug use based on standards of appropriateness.
- Develop a mechanism for evaluating the impact of review.

It should be emphasized, however that this is only a conceptual model that can serve as framework for performing DUR (Serfontein, 1996:33).

3.2.7 Drug classification systems

A drug classification system represents a common language for describing the drug in a country or region and is a prerequisite for national and international comparisons of drug utilisation data, which have to be collected and aggregated in a uniform way. Access to standardised and validated information on drug use is essential to allow audits of patterns of drug utilisation, to identify problems in drug use, to initiate educational or other interventions and to monitor the outcomes of the interventions (Sjöqvist & Birkett, 2003).

Refer to chapter 4 section 4.8.1 for the drug classification systems used in this study.

3.2.8 Units of measurement

Drug utilisation studies are measured in either the daily defined dose or the prescribed daily dose:

3.2.8.1 Daily defined dose (DDD)

The daily defined dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults (Sjöqvist & Birkett, 2003). It was developed in response to the need to convert and standardise readily available volume data from sales statistics or pharmacy inventory data (quantity of packages, tablets, or other dosage forms) into medically meaningful units, to make crude estimates of the number of persons exposed to a particular drug or class of drugs (Lee & Bergman, 1994:386) (refer to section 3.2.8.2). The WHO (2003b) further emphasized that the DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose (PDD). Doses for individual patients and patient

groups will often differ from the DDD as they must be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.

- **The advantages of using DDD include (Lee & Bergman, 1994:386):**

❖ Its usefulness for working with readily available gross drug statistics at various levels of the health chain; as a standardized unit of measurement.

❖ Comparisons are drawn between drugs in the same therapeutic class and between different health care settings or geographic areas.

❖ The evaluations of trends over time.

- **The defined daily dose also has some limitations (Lee & Bergman, 1994:387):**

❖ The DDD is not a recommended dose, but rather a technical unit of comparison.

❖ Problems arise when dosages vary widely (antibiotics), when one drug is used for more than one indication, or when drugs are used in combination with other drugs for the same disease.

❖ The DDDs do not take into account paediatric uses. Since children's doses are substantially lower than the established DDDs, this will lead to an underestimation of population exposures which may be significant in countries with a large paediatric population.

❖ DDDs do not take into account variations in compliance.

3.2.8.2 Prescribed daily dose (PDD)

According to Sjöqvist and Birkett (2003) the prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD can be determined from prescription studies and medical-or pharmacy records. It is important to relate the PDD to the diagnosis for which the dosage is based. The PDD will give the average daily amount of a drug that is actually prescribed.

Sjöqvist and Birkett (2003) also mentioned that it should be noted that the prescribed daily dose does not necessarily reflect actual drug utilisation. This is due to the fact that some prescribed medications are not dispensed, and also the patient does not always take all the medications that are dispensed. Special studies including patient interviews are required to measure actual drug intake at the patient level (i.e. consumed daily dose). The PDD will also differ for different indications of the same drug, so it will sometimes be necessary to reach this level of detail to interpret overall use data (WHO,2003b).

3.2.9 Limitations of DUR

The greatest limitation of the DUR process, according to Enright and Flagstad (1991:1910) is that in many cases it has become the end, not the means, of examining the quality of drug use. DUR has also frequently been used more as a club than as a tool. Findings are often confusing, incomplete, or non-specific, making it difficult to formulate a corrective action plan.

3.2.10 DUR and pharmacoeconomics

The use of utilisation studies in conjunction with pharmacoeconomic analysis can result in more cost-effective utilisation of medicines and a better utilisation of pharmacoeconomic methods, both of which contribute to a more rational use of drugs (Sacristan & Soto, 1994:299).

Drug utilisation review (DUR) and pharmacoeconomics both concern the consumption patterns of drugs, and their implications. Since DUR and pharmacoeconomics interact and integrate each other, a review of the literature on both represents a useful opportunity for underlining the role of DUR in fostering and broadening the scope and the effectiveness of the new discipline of pharmacoeconomics (Garattini & Tognoni, 1993:162). Despite having distinctly different methodologies, both drug utilisation studies and pharmacoeconomic studies incorporate economic and social perspectives. The optimal usage of resources and the most rational use of drugs are their main objectives (Sacristan & Soto, 1994:300).

It is also interesting to see that both definitions of pharmacoeconomics and drug utilisation studies include the terms "society", as well as an economic term. Both methods therefore clearly emphasise socio-economic factors (Truter, 1997:19).

It is also important to remember that when classifying different methods of study (clinical trials, epidemiological studies, drug surveillance systems, pharmacoeconomic studies and drug utilisation studies) the objective is to obtain a greater understanding of the properties of the drugs that we use and to obtain a more rational usage. All of the above methods must be considered as complementary, rather than attempting to demonstrate the power of one over the other (Sacristan & Soto, 1994:309).

Clinical trials, whose main objective is to show beneficial and adverse effects of a drug before it is launched, can also be used to calculate the costs of different alternatives. Drug utilisation studies, which are utilised to study the adverse effects of drugs after launching, must be implemented to study their benefits and treatment costs under real-world conditions (Sacristan & Soto, 1994:309).

It is therefore not surprising that pharmacoeocnomic studies and drug utilisation studies are related, nor that both can utilise, directly or indirectly, parts of the elements of the other.

Pharmacoeconomic evaluations are also aimed at determining the efficiency of the interventions, and, carried out in the context of DUR programmes, can be used to discover the profitability of such interventions and to help select the most efficient ones (Sacristan & Soto, 1994:310).

3.2.10.1 DUR and pharmacoeconomics in developing countries

Garattini and Tognoni (1993:168) mentioned that DUR and pharmacoeconomics have developed in, and require a background of, healthcare settings and markets that allow free choices to be made to optimise use and expenditures. The countries of the "economic South" of the world are characterised by increasing scarcity of resoucres. In this context the meaning of the term DUR-pharmacoeconomics changes completely. DUR should focus on the specific conditions of the countries, whose main problem is the impact of the relative unavailability of drugs on the health of the population. Pharmacoeconomics should favour the production of rational, economically efficient drug policies, rather than principally cost-containment strategies.

3.2.11 Summary

The study of drug utilisation is still evolving, and the opportunities for the study of drug utilisation have been virtually unexplored, but the political issue regarding the confidentiality of medical records, as well as the shortage of funds and labour in the current era of cost-containment, will set the constraints which will shape the future of the study of drug utilisation (Lee & Berman, 1994:389).

Serfontein (1996:13) further stated that if DUR is done correctly it can be a powerful tool that can be used to analyse the appropriateness of drugs prescribed by doctors. For any DUR programme to be successful it is very important that the co-operation of all the role players be obtained. The objectives of a DUR programme would be missed if the programme is seen as a tool to punish the doctors every time a prescription does not meet the criteria. DUR should be viewed by the doctors as an ongoing educational process that will help them to better the quality of health care they render to their patient.

3.3 Managed health care

3.3.1 Introduction

During 1995 managed care was introduced to this country. It was soon discovered that implementation of managed care involves many highly charged and emotive issues. The aim of

introducing managed care to South Africa was to control costs and there are some examples of successes. Patient admissions to hospitals have decreased but the cost per admission has risen (Rothberg *et al.*, 1999?).

During the latter part of 1995, South Africa's health care providers were informed by the Medical Association of South Africa (MASA), the Representative Association of Medical Schemes (RAMS) and major business entities (Anglo-American, Southern Life and Sanlam) that Managed Healthcare was about to transform the private sector (Rothberg *et al.*, 1999?).

To utilisation-review organisations (UROs), managed care means monitoring the delivering of health care in all delivery systems and at all delivery sites; which includes all contacts between patient and provider (Becker, 1990:2274).

3.3.2 Nature of managed care

Managed care refers to a variety of methods of financing and organising the delivery of comprehensive health care in which an attempt is made to control costs by controlling the provision of services (Iglehart, 1994:1167). One of the goals of managed care is then to improve the efficiency of the delivery of care without having a negative impact on the quality of care provided (Becker, 1990:2274); making provision for (Becker, 1990:2275-2276):

- Hospital preadmission certification programmes
- Second surgical opinions
- Medical case management

The dimensions of managed care interact in the attempt to deliver quality health care while containing costs, but when all of the rhetoric is stripped away the common denominator is doctors. Managed care works through the actions of doctors (or other professionals initiating care) to eliminate inappropriate treatments and ensure that cost effective practice is adopted (Fairfield *et al.*, 1997:1825).

3.3.3 Advantages of managed care

There are several advantages of managed care, includes that (Health Care Financing Administration, 1996):

- It's easier to budget medical costs because he/she knows what amount of any premiums in advance, and total of other out-of-pocket expenses, is likely to be less than the fee-for-service.

- The patient generally pays a normal co-payment when they use a service. Some plans do not charge co-payments for certain specified services.
- Paperwork is virtually eliminated.

3.3.4 Disadvantages of managed care

There are also a number of disadvantages of managed care, which include the following (Health Care Financing Administration, 1996):

- The patient may not be free to go to any physician or hospital they choose. Except, when they need emergency or unforeseen out-of-area urgent care services, you generally must use the plan's providers or else the plan will not pay.
- The patient may need to have the prior approval of his/her primary physician to see a specialist, have elective surgery, or obtain equipment or other medical services.
- It can take up to 30 days to disenroll, and the patient must continue to use the HMO* providers until they are disenrolled.

3.3.5 Managed care and pharmacoeconomics

According to Stergachis *et al.* (1996:247), managed care plans are beginning to use methodologies of pharmacoeconomics and pharmacoepidemiology to improve decision-making. Illustration of the application of pharmacoeconomics to managed care is categorized into three general areas:

- Formulary policy
- Prescriber and pharmacist practices
- Drug benefit design.

3.3.6 Summary

Rothberg *et al.* (1999?), concluded that the past five years have witnessed the complicated delivery and development of integrated managed care in South Africa. Attendants at the birth were ambivalent about its viability, and several would have felt comfortable with withdrawal of all life-support. However, managed care has become ambulant and is taking steps with increasing confidence.

* Health Management Organization

Rothberg *et al.* (1999) further added that health funding is not under control and that there is still a great deal of work to be done if managed care is to impact on health care costs and bring them down.

3.4 Medicine pricing

3.4.1 Introduction

According to Tshabalala-Msimang (2004:5) the whole purpose of the Medicines Control Amendment Act of 1997 is to make medicines affordable to the people of South Africa and to improve practices relating to the manufacture and sale of medicines. In addition to this, these regulations are a landmark in terms of reducing the price of medicines. According to the Free Market Foundation (2006:1), one of government's motivations for requiring a single exit price for medicines is to ensure that "South Africans have access to affordable, good quality medicine" (Free Market Foundation, 2006).

In contrast to this the Free Market Foundation (2006) also mentioned that South Africa appears to be generally well served by its medicine suppliers and drastic government intervention such as the institution of price controls is unwarranted.

3.4.2 Single exit price (SEP)

Single exit price means the price set by the manufacturer or importer of a medicine or scheduled substance in terms of these regulations combined with the logistics fee and VAT and is the price of the lowest unit of the medicine or Scheduled substance within a pack multiplied by the number of units per pack (SA, 2004:6).

3.4.2.1 Method for setting the single exit price

The draft regulations require that manufacturers set the single exit price at 50% below the official listed price contained in a publication know as the "Blue Book". According to Osman (2004) the final regulations specify that:

- The level of the exit price will be determined on a product-by-product basis.
- The single exit price will be determined in two phases. In phase 1 the single exit price will be the net price at which medicine is currently being sold. In phase 2 the benchmark for the single exit price will be based on an international price, calculated according to a prescribed formula. Phase 2 will probably commence at the end of this year (2004) or early 2005.

- New products will use international pricing as the benchmark from the date of launch. This change in approach rests firmly on the hard evidence secured during the comment period – information never being accessed before – of hugely different mark-ups across pharmaceutical companies. In a few cases, products were selling below the international average. At the opposite side of the spectrum, products were selling 80% above the international price. Clearly it was not fair and it simply would not work to impose a simple, undifferentiated formula across the board.

3.4.2.2 Calculating the single exit price

The price of each medicine or Scheduled substance to be set upon the date of commencement of these regulations by the manufacturer or importer must not be higher (SA, 2004:8) –

- In respect of a Scheduled substance that is not a medicine, than the weighted average net selling price per unit of each Scheduled substance for the calendar year 2003: Where sales of the scheduled substance commenced at the beginning of January 2004 or thereafter, the price of such substance must be calculated using the average of the total rand value of sales less the total rand value of the discounts for the period for which the Scheduled substance was sold and with reference to the price of that Scheduled substance in other countries in which the prices of medicines and Scheduled substances are regulated and published;
- In respect of a medicine, than the weighted average net selling price of the medicine which must be calculated using the formula:

"S divided by the total number of lowest units (e.g. a tablet) for all of the packs of the same dosage strength of the medicine sold in the year 2003". Where S = the total rand value of net sales (being sales less discounts) for all packs of the same dosage strength of the medicine sold in the year: provided that were sales of the medicine commenced at the beginning of January 2004 or thereafter, the price of the medicine must be calculated using the average of the total rand value of sales less the total rand value of the discounts for the period for which the medicine was sold and with reference to the price of that medicine in other countries in which prices of medicines and Scheduled substances are regulated and published (SA, 2004:9).

3.4.2.3 Implementation of pricing regulations

The regulations specify that wholesalers, distributors and retailers (community pharmacies) from 2 August 2004 are allowed to sell, medicine only in accordance with the provisions of the regulations. This permits a 3 month period to phase the regulations in and to sort out technical issues. While the regulations make provision for the old and new systems to run in parallel, this

is clearly not practical, particularly when considering information technology systems (Osman, 2004).

For community pharmacies, these regulations specify that from 2 August 2004 schedule 0 medicines may be sold with the traditional markup that is currently used. Schedule 1 and 2 substances sold over the counter, i.e. without a doctor's prescription, will be sold with a dispensing fee of 16%, capped at R16 when the SEP of a product is more than R100 (Osman, 2004).

Osman (2004) added that when sold on prescription, Schedule 1 to 6 medicines will be sold at a dispensing fee of 26%, capped at R26 when the SEP is more than R100. The SEP is inclusive of the distribution fee and exclusive of value-added-tax (VAT).

The provisions of this regulation 10 must be reviewed annually by the Minister with regard to the CPI[#] the PPI[*], and the need to ensure the availability, affordability and quality of medicines and Scheduled substances in the Republic (SA, 2004:14).

3.4.2.4 Supreme court appeal

Subsequently the Pharmaceutical Society of South Africa (PSSA) and other including the Pharmaceutical Manufacturers Association (PMA) challenged the regulations in the Cape High Court and the Supreme Court of Appeal (SCA). A full bench of the Supreme Court of Appeal ruled in favour of the PSSA and its partners on 20 December 2004. The SCA unanimously agreed that the pricing regulations should be set aside, and that the Department of Health should pay all legal costs (Bester & Hammann, 2005).

In addition to this the Constitutional Court judgement of 30 September 2005 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 availability of retail pharmacies (especially rural and courier pharmacies) (Tshabalala-Msimang, 2006).

The effect of the judgement is that the regulated Single Exit Price and the dispensing fee are no longer in operation. Pharmacists and doctors may now charge any fee that will cover the costs of dispensing (Bester & Hammann, 2005).

The influence of these pricing regulations prior, during and after implementation will be illustrated on the cost and prescribing patterns of ACE inhibitors in chapter 5.

[#] Consumer Price Index
[*] Production Price Index

3.4.2.5 Expected savings with single exit price

The **expected** savings with the single exit price on medicine are illustrated below (Beaumont, 2004:25):

EXPECTED SAVINGS	
On branded ex factory medicines:	15%
On generic medicines ex factory:	30%
Overall ex factory:	25-30%
After a year:	costs down one third
Total across the board:	40-50%

Figure 3.3: Expected saving with single exit price (Beaumont, 2004:25)

These expected savings will be illustrated in chapter 5 to see what the real savings are for ACE inhibitors.

3.4.3 The effect of price controls

The most fundamental problem with price controls, whether they are for medicines or for any other product, is that they interfere with the normal pricing mechanism and the signals that prices send to buyers and sellers. Price controls distort that pricing mechanism and interrupt the dynamic demand and supply process. Consumer tastes and needs change continuously and as demand for a particular product rises or falls, so the price rises and falls, sending signals to manufacturers to adjust the supply of the product in a never-ending trend towards an equilibrium price (Free Market Foundation, 2006).

3.4.4 Consequences of price control

The Free Market Foundation (2006) is also of the opinion that by interfering in the normal market process, price controls discourage normal price competition and stifle innovation, research and development. Without any normal price signals, manufacturers cannot respond to the needs of consumers and are therefore often unwilling or unable to improve their product and to comply effectively in order to meet the needs of the consumers.

It may be argued that healthcare and medicines are somehow different from other goods and that therefore price controls are justified. The market for medicine and healthcare, however, is subject to the same laws of economics as any other good or service. In fact, given the importance of good healthcare for human well-being and the highly damaging effects of price controls, it is imperative that price controls are NOT imposed on medicines (Free Market Foundation, 2006).

The question remains who is the main decision maker in the prescribing of medicine: the patient, the prescriber, or the third party payer?

3.4.5 Conclusion

The new system will take some time to move into top gear. When it does, South African consumers will find themselves on an equal footing with some other countries where the price of medicines is controlled. A year from now we should be paying nearly a third less, on average, for generic and brand-name products (Tshabalala-Msimang, 2004).

While the government may have good intentions in wanting to increase access to medicines and good quality healthcare, the imposition of a SEP is having many unintended consequences, which are reducing access to medicines and compromising South Africa's healthcare system (Free Market Foundation, 2006). Furthermore, the influence of the SEP in this study will be compared with regard to different "prices".

3.5 Chapter summary

This chapter contained an overview of pharmacoeconomics, drug utilisation review as well as managed care. Furthermore, an overview of the new pricing regulations was discussed, as well as the implementation thereof and the expected reduction in medicine pricing. The latter form is considered an important part of this study.

Chapter 4 will contain the empirical investigation of this study.

Chapter 4

Objectives and methodology

4.1 Introduction

In this chapter the research objectives of both the literature and the empirical investigation are discussed, as well as the research methodology followed in this study.

4.2 Research objectives

The research objectives of this study consist of both general and specific research objectives.

4.2.1 General research objectives

The general research objectives of this study are to investigate the prescribing patterns, cost the possible effect of generic substitution on the prescribing patterns of ACE inhibitors in South Africa for the period 2001 until 2006.

4.2.2 Specific research objectives

4.2.2.1 The specific research objectives of the literature study include the following (also refer to chapter 1):

- Discuss the management of hypertension, congestive heart failure and other cardiovascular diseases, with emphasis on ACE inhibitors in these diseases according to literature.
- Determine the prevalence of hypertension and congestive heart failure according to literature.
- Describe what the "new" pricing regulations (implemented in 2004) entail.
- Indicate the relevance of using, as well as the way to use, combination therapy in conjunction with ACE inhibitors for cardiovascular diseases, according to literature.

- Describe what the basic aspects of pharmacoeconomics entail.
- Indicate the fundamentals of drug utilisation review and managed care.
- Determine the basic aspects and use of generic substitution.

4.2.2.2 The specific research objectives of the empirical investigation

The specific research objectives of the empirical investigation are to:

- Determine the overall cost and prescribing patterns of all medicine items on the total database including cardiovascular, antihypertensive and ACE inhibitor items.
- Determine the cost and overall prescribing patterns of innovator and generic products from the total database with reference to cardiovascular, antihypertensive and ACE inhibitor items.
- Determine the potential savings of all medicine item costs with regard to the single exit price (SEP) (refer to chapter 3, section 3.4.2.5).
- Investigate the prevalence of ACE inhibitor active ingredients
- Investigate the prevalence percentage by which ACE inhibitors form part of all the antihypertensive as well as cardiovascular items.
- Investigate the cost analyses of the top 20 ACE inhibitors according to prevalence
- Determine the prevalence and cost of the individual ACE inhibitor items
- Determine what new ACE inhibitor trade names appeared on the market during the appropriate study periods.
- Investigate the combination of ACE inhibitors and other antihypertensive products on the same prescription
- Reveal the number of prescriptions per patient containing at least one ACE inhibitor
- Determine the prescribed daily dose (PDD) and effect sizes between ACE inhibitor active ingredient innovators and generics.
- Determining the ACE inhibitors on the list of top 50 products of Interpharm® Datasystems and comparing these to the ACE inhibitors on the list of top 50 products of Mediscor®, according to prevalence and cost.

4.3 Research design

The research design consists of a retrospective drug utilization study (also refer to chapter 3, section 3.2.5) that was done by classifying the different ACE inhibitors into their respective pharmacological active ingredients as well as their innovator or generic status. These data were provided by Interpharm Datasystems® (Pty.) Ltd., as well as Mediscor® Pharmaceutical benefit management company (the data from Mediscor® were only used in chapter 5, section 5.10).

4.4 Research methodology

The research methodology consists of the following steps:

- Selecting the appropriate data.
- Selecting the appropriate measuring instruments (refer to 4.9)
- Obtaining the data (refer to 4.7)
- Conducting a data analysis (refer to 4.8)
- Results and discussion of results of the empirical investigation (refer to 4.2.2.2 for research objectives).

4.5 Study population

The study population was selected according to ACE inhibitors used by patients. The items contain either single (one active ingredient) or combination (more than one active ingredient) ACE inhibitors. A total of 197 771 prescriptions containing ACE inhibitors that represent the study population for the period 2001-2002 are analysed.

For the period 2004, a total of 182 970 prescriptions are analysed that represent the study population and for 2005 a total of 105 117 prescriptions containing ACE inhibitors are analysed. The study period of 2006 is represented with 55 667 prescriptions that are analysed.

4.6 Database

A quantitative, retrospective study is done on data provided by a medicine claims database, Interpharm Datasystems®(Pty.) Ltd. for the period 2001 until 2006.

The following fields are used in this study:

- The active ingredient of the drug

- The NAPPI code of the drug
- The cost of the drug
- The number of prescriptions dispensed
- Period in which the item was dispensed
- Indication whether the item is a single agent or combination agent, and whether the items are innovator or generic medicine items.
- The number of tablets and capsules prescribed.
- Medical scheme code
- Medical scheme dependant code.

4.7 Data source

The data are extracted from Interpharm Data Systems® (Pty.) Ltd. The data are divided into a study period from 1 January 2001 to 31 December 2002, and are conducted on a two yearly basis. Data are also extracted for the period 2004, 2005 and 2006 and these are further divided from January to April, May to August and September to December. The data from 2003 as well as aspects on age and gender are not available in electronic format and therefore not included in this study. For the period prior to September 2004 there were no changes in pricing regulations and this is known as the pre-implementation phase. The period from September 2004 to December 2004 is known as the implementation phase, and the period after December 2004 is known as the post-implementation phase, referring in all cases to the introduction of the SEP.

Note that the years 2001-2002 are combined as one study period which will only be used as a control and will not be compared to the other study periods, because there were no changes in pricing legislation that could have influenced changes in pricing.

4.8 Data analysis

The medicine are analysed with regard to different classification systems:

4.8.1 Classification systems

For the purpose of this study, different classification systems are used.

4.8.1.1 NAPPI codes

The NAPPI (National Approved Product Pricing Index) codes are unique nine digit product codes implemented with electronic transactions in mind. Product name, pack size, strength, manufacturer plus exclusions etc. are incorporated (Snyman, 2005:7a). The individual products are identified by using the NAPPI code.

4.8.1.2 Classification according to active ingredient

The chemical classification is done by using the MIMS® (Monthly Index of Medical Specialities), where agents are listed according to active ingredients and trade names (Snyman, 2005:7a). classification group 7 was used for cardiovascular items, group 7.3 for antihypertensive items and 7.3.8 for ACE inhibitor items.

4.8.2 Statistical methods used

The statistical analysis methods used in this empirical investigation will be discussed below:

4.8.2.1 Software used

Data are analysed by using the Statistical Analysis System (SAS® for Windows, 9.1, 2006)

4.8.2.2 Arithmetic mean (average)

Brase and Brase (1999:94) stated that an average that uses the exact value of each entry is the *mean* (sometimes called the *arithmetic mean*). To compute the mean, the values of all the entries are added and then divided by the number of entries.

The mean can be calculated by using the following formula (Kirkwood, 1988:12):

$$\text{Mean, } \bar{x} = \frac{\Sigma x}{n}$$

Where:

x = values of the variable.

$\sum$ = the sum of.

n = number of observations.

4.8.2.3 Standard deviation

Barlo (2007) stated that the deviation value represents the average distance of a set of scores from the mean. Kirkwood (1988:14) defined the standard deviation as taking the *square root* of the variance. The standard deviation can be calculated by using the following formula (Kirkwood, 1988:14):

$$\text{s.d., } s = \sqrt{\left[\frac{\Sigma(x-\bar{x})^2}{(n-1)}\right]}$$

or equivalently

$$s = \sqrt{\left[\frac{\Sigma x^2 - (\Sigma x)^2/n}{(n-1)}\right]}$$

Where:

S = standard deviation

$\sum$ = the sum of.

x = values of the variable.

n = number of observations.

4.8.2.4 Cost-prevalence index

The cost-prevalence index can be used as an indication to show the relation between the number of medicine items per prescription and the total medicine cost (Serfontein, 1989:180).

The cost – prevalence index can be calculated by using the following formula:

$$\text{Cost – prevalence index} = \frac{\text{Cost \%}}{\text{Prevalence \%}}$$

Where:

- **Cost index >1**: Shows that the therapy is relatively expensive.
- **Cost index =1**: Shows equilibrium between the cost and prevalence of the therapy.
- **Cost index <1**: Shows that the therapy is relatively inexpensive.

4.8.2.5 Effect sizes (d-values)

Talheimer and Cook (2002) stated that an effect size is the difference between two means divided by the standard deviation of the two conditions. The effect sizes can be calculated by using the following formula:

$$d = \frac{x_t - x_c}{S_{max}}$$

Where:

- **d** = effect size
- x_t = average cost of treatment (mean)
- x_c = average cost of comparison treatment (mean)
- S_{max} = maximum standard deviation.

The following guidelines can be used to evaluate the d-values (Steyn, 1999:3):

- ***d*** = 0.2: small effect – no significance.
- ***d*** = 0.5: medium effect – observable and may give significant results.
- ***d*** = 0.8: big effect – the results are significant and of practical importance.

4.8.2.6 Median

The median of a set of observations is the value that falls in the middle (50%) when the observations are arranged in order of magnitude (Keller & Warrack, 2000:93).

The median can be illustrated by using the following formula (Keller & Warrack, 2000:93):

Given *n* observations arranged in order of magnitude, Median = Middle value, if *n* is odd ***or*** Mean of the two middle values, if *n* is even

4.9 Measuring instruments

The different measuring instruments used in this study will be defined below:

Frequency: The frequency for a data value is the number of times the value occurs in the data set (Jaisingh, 2000:6). In this study, frequency and prevalence are viewed as synonymous.

In this study all aspects regarding frequency were analysed as follows:

- Number of items per prescription for all study periods
- Prevalence of innovator and generic products from the total database with specific reference to cardiovascular, antihypertensive and ACE inhibitor medicine items
- Prevalence of ACE inhibitor active ingredients
- Prevalence of ACE inhibitors as percentage of cardiovascular and antihypertensive items
- Usage patterns of the individual ACE inhibitor items
- Identifying new ACE inhibitors on the market
- Investigating the combination of ACE inhibitors and other antihypertensive products on the same prescription

- Number of prescriptions per patient containing at least one ACE inhibitor
- Determining the prescribed daily dose (PDD) between innovator and generic ACE inhibitor active ingredients.
- Determining ACE inhibitors in the list of top 50 products of Interpharm® Datasystems and comparing it to the ACE inhibitors on the list of top 50 products Mediscor®, according to prevalence.

Cost: Refer to chapter 3, section 3.1.5.

In this study all aspects regarding cost are analysed as follows:

- Total and average cost per prescription and cost per medicine item
- Cost of innovator and generic products from the total database with reference to cardiovascular, antihypertensive and ACE inhibitor medicine items
- Expected cost savings with regard to the single exit price (SEP)
- Cost analyses of the top 20 ACE inhibitors
- Cost of the individual ACE inhibitor items

4.10 Ethical aspects

Approval was obtained for the study from the Pharmacy Benefit Management (PBM) as well as from the research committee of the North-West University to conduct this drug utilization study. Data used in the analyses were obtained where 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. Therefore, no specific patient, medical practice, pharmacy or medical scheme could be identified and confidentiality of information was maintained throughout the study.

4.11 Results and discussion

The results and discussion of the empirical investigation will be discussed in chapter 5.

4.12 Conclusion and recommendations

The conclusion and recommendations of this study will be discussed in chapter 6.

4.13 Chapter summary

In this chapter the research objectives of both the literature and empirical investigations were discussed. The chapter also contained a discussion of the research methodology and design, as well as the statistical methods and data analysis done on this study.

Chapter 5 will contain the results and discussion of the empirical research objectives.

Chapter 5

Results and discussion

In this chapter the results of the empirical investigation are discussed. The results are presented according to the specific study periods: from 2001-2002, 2004, 2005 and 2006. The year periods 2004 until 2006 are further divided into four monthly periods from January to April, May to August and from September to December for 2004, 2005 and 2006.

The results are reported and discussed according to the following categories:

- The prevalence and cost of all medicine items on the total database.
- Comparing the cost and prevalence of all innovator and generic items on the total database with reference to cardiovascular, antihypertensive and ACE inhibitor items.
- Cost savings of all medicine items and ACE inhibitors with regard to the single exit price (SEP).
- Prevalence of ACE inhibitor active ingredients.
- Prevalence percentage of ACE inhibitors with regard to cardiovascular items.
- Prevalence percentage of ACE inhibitors with regard to antihypertensive items.
- The cost analysis of the top 20 prescribed individual ACE inhibitors according to prevalence.
- The prevalence and cost of individual ACE inhibitors with regard to their status as single or combination items, as well as their status as innovator or generic items.
- The new ACE inhibitors on the market.
- Combination of ACE inhibitors and other antihypertensive products on the same prescription.
- Prescribed daily dose and effect size of innovator and generic ACE inhibitor active ingredients.
- Comparing the prevalence of ACE inhibitors in the top 50 list of Mediscor® database with the top 50 list of Interpharm® for 2002, 2004, 2005 and 2006.

Figure 5.1 provides an overview of the presentation of the results.

* *Note that all ACE inhibitor items in this chapter as well as in the appendices are the items that were available on the South African market and claimed through the medicine claims database. There may be medicine items that are on the South African market, but were not claimed during the study period through the medicine claims database and are thus not included in this study.**

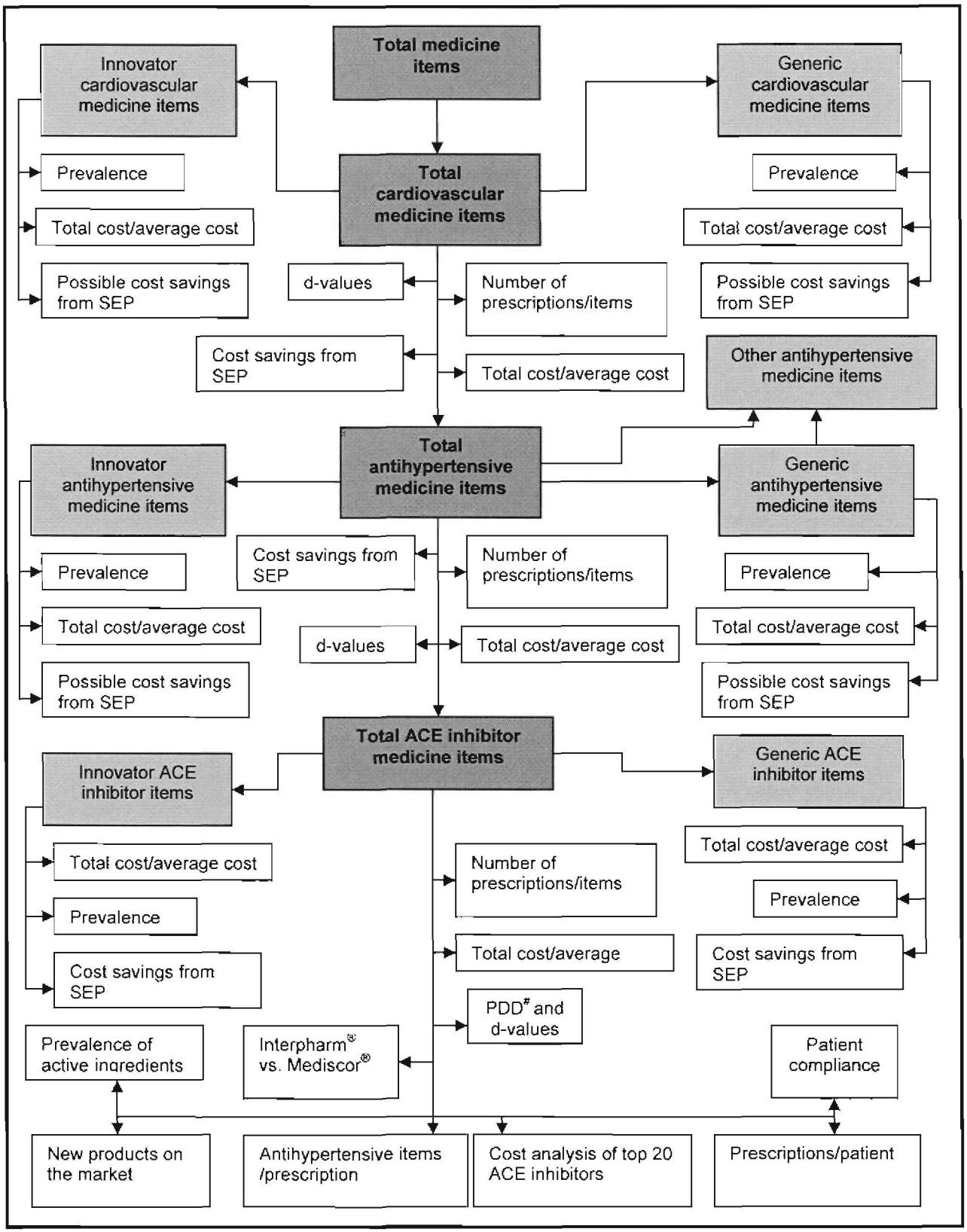

Figure 5.1: Illustration of the presentation of the results

Prescribed daily dose

5.1 Definitions

Certain terms used in this study and chapter are defined below:

Active ingredient: For the purpose of this study an active ingredient refers to the pharmacological ingredient for the treatment or prevention of disease.

Combination items: Combination items are made up of two or more active pharmacological ingredients in the same dosage form (SA, 2006:11) (Also refer to chapter 2, section 2.3).

Database: Database refers to medicine items recorded through medicine claims. It may be the total in different categories for example: total medicine items claimed, cardiovascular, antihypertensive or ACE inhibitor items.

Generic items: These are medicines, registered in South Africa, where such a medicine 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) (Also refer to chapter 2, section 2.4). Generic medicine items are therefore assumed to be identical in dose, strength, route of administration, safety, efficacy and intended use as the original patented medicine (innovator) (Rognehaugh, 1998:91).

HCTZ: This abbreviation will be used for hydrochlorothiazide throughout this chapter and in the appendices.

Innovator items: These are medicines that are registered in South Africa, where such medicine is currently protected by a patent or had been protected by a patent previously. Such medicines may be marketed either by the original patent holder or another entity (SA, 2006:8).

Patient: A patient is an individual who used medication to prevent or treat an illness and who received one or more of the prescriptions on the database.

Prescription: A prescription is a written instruction by a prescriber by law of what medicine the patient must be given to prevent or treat an illness, and may consist of one or more medicine items.

Single item: A single item is a medicine item which consists of only one active pharmacological ingredient.

*The terms *product* and *item* can be considered to be synonymous for the duration of this study.*

5.1.1 Data analysis of the total database

This section will address the cost and prevalence of all medicine items claimed through the medicine claims database.

5.1.1.1 Number of items per prescription

5.1.1.1.1 Introduction

In this section the number of items per prescription discussed for cardiovascular, antihypertensive and ACE inhibitor items is summarised in table 5.1. Furthermore, the percentages of the cardiovascular, antihypertensive and ACE inhibitor items and prescriptions as part of the total database are also discussed and summarised in table 5.1.1 to 5.1.4 for the respective periods from 2001 until 2006.

Table 5.1: Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitors from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
2001-2002	**Total database**	Number of medicine items/prescription	3551616*	1.97	1.17	6 993 471
	Cardiovascular items	Number of cardiovascular items/prescription	515255*	1.43	0.71	139 049
	Antihypertensive items	Number of antihypertensive items/prescription	386820*	1.21	0.47	87 377
	ACE inhibitors	Number of ACE inhibitors/prescription	197771*	1.01	0.08	195 937
	Total database	Cost/prescription (R)	3551616*	276.23	320.65	981 058 814.00
		Cost/ medicine item (R)	6993471	140.28	184.92	981 058 814.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	515255*	231.61	165.05	172 210 489.00
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	386820*	202.32	130.95	97 677 845.31
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	197771*	200.20	82.00	38 999 080.33
2004	**Total database**	Number of medicine items/prescription	2595242*	2.04	1.27	5 305 846
	Cardiovascular items	Number of cardiovascular items/prescription	515255*	1.41	0.70	725 778
	Antihypertensive items	Number of antihypertensive items/prescription	372563*	1.19	0.44	441 613
	ACE inhibitors	Number of ACE inhibitors/prescription	182970*	1.01	0.08	184 018
	Total database	Cost/prescription (R)	2595242*	254.78	397.84	661 221 000 .00
		Cost/medicine item (R)	5305846	124.62	228.55	661 221 000.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	515255*	248.47	183.95	128 023 228.00
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	372563*	218.81	145.19	81 520 365.83
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	182970*	159.04	89.47	29 100 326.90

* Number of prescriptions
** Total number of items or total cost of items as applicable

Table 5.1 (continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitors from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
2005	**Total database**	Number of medicine items/prescription	1621739*	2.22	1.37	3 606 992
	Cardiovascular items	Number of cardiovascular items/prescription	293694*	1.41	0.70	415 559
	Antihypertensive items	Number of antihypertensive items/prescription	216354*	1.20	0.47	260 376
	ACE inhibitors	Number of ACE inhibitors/prescription	105117*	1.00	0.07	105 571
	Total database	Cost/prescription (R)	1621739*	250.24	403.60	405 829 097.00
		Cost/ medicine item (R)	3606992	112.51	226.99	405 829 097.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	293694*	230.82	167.45	67 791 492.95
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	216354*	202.96	132.21	43 910 503.79
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	105117*	151.20	80.55	15 893 890.26
2006	**Total database**	Number of medicine items/prescription	996787*	2.38	1.44	2 370 572
	Cardiovascular items	Number of cardiovascular items/prescription	159584*	1.41	0.69	225 112
	Antihypertensive items	Number of antihypertensive items/prescription	121721*	1.24	0.50	150 821
	ACE inhibitors	Number of ACE inhibitors/prescription	55667*	1.00	0.07	55 910
	Total database	Cost/prescription (R)	996787*	280.06	434.37	279 160 832.00
		Cost/ medicine item (R)	2370572	117.76	237.81	279 160 832.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	159584*	262.40	186.24	41 874 792.33
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	121721*	234.21	144.85	28 508 628.11
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	55667*	171.60	72.76	9 552 425.76

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1(continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitors from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Jan-Apr 2004	**Total database**	Number of medicine items/prescription	713470*	1.91	1.21	1 363 571
	Cardiovascular items	Number of cardiovascular items/prescription	145232*	1.40	0.69	203 413
	Antihypertensive items	Number of antihypertensive items/prescription	104335*	1.19	0.44	123 763
	ACE inhibitors	Number of ACE inhibitors/prescription	50107*	1.01	0.07	50 360
	Total Database	Cost/prescription (R)	713470*	278.83	476.38	198 933 607.00
		Cost/ medicine item (R)	1363571	145.89	283.72	198 933 607.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	145232*	288.85	203.48	41 950 474.27
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	104335*	256.08	158.94	26 718 220.57
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	50107*	187.69	98.21	9 404 465.25
May-Aug 2004	**Total database**	Number of medicine items/prescription	935640*	2.09	1.29	1 953 833
	Cardiovascular items	Number of cardiovascular items/prescription	170917*	1.40	0.69	239 798
	Antihypertensive items	Number of antihypertensive items/prescription	123486*	1.18	0.44	146 293
	ACE inhibitors	Number of ACE inhibitors/prescription	60328*	1.01	0.07	60 661
	Total **Database**	Cost/prescription (R)	935640*	259.42	370.98	242 720 711.00
		Cost/ medicine item (R)	1953833	124.23	208.03	242 720 711.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	170917*	255.91	187.50	43 738 731.52
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	123486*	225.60	147.91	27 858 238.13
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	60328*	163.62	90.31	9 870 673.88

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1 (continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitors from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Sept-Dec 2004	**Total database**	Number of medicine items/prescription	946132*	2.10	1.30	1 988 422
	Cardiovascular items	Number of antihypertensive items/prescription	144742*	1.19	0.44	171 557
	Antihypertensive items	Number of cardiovascular items/prescription	199106*	1.42	0.71	282 567
	ACE inhibitors	Number of ACE inhibitors/prescription	72535*	1.01	0.08	72 997
	Total database	Cost/prescription (R)	946132*	232.07	354.89	219 566 683.00
		Cost/ medicine item (R)	1988442	110.42	202.84	219 566 683.00
	Cardiovascular items	Cost/prescription containing cardiovascular item(s) (R)	199106*	212.62	157.05	42 334 022.38
	Antihypertensive items	Cost/prescription containing antihypertensive item(s) (R)	144742*	186.15	123.62	26 943 907.13
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	72535*	135.45	74.89	9 825 187.77

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1 (continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitors from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Jan - Apr 2005	Total database	Number of medicine items/prescription	517926*	2.17	1.35	1 124 635
	Cardiovascular items	Number of cardiovascular items/prescription	91806*	1.40	0.69	128 902
	Antihypertensive items	Number of antihypertensive items/prescription	67287*	1.19	0.45	80 379
	ACE inhibitors	Number of ACE inhibitors/prescription	32622*	1.00	0.07	32 763
	Total Database	Cost/prescription (R)	517926*	245.63	376.04	127 217 012.00
		Cost/ medicine item (R)	1124635	113.12	209.13	127 217 012.00
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	91806*	231.10	168.48	21 216 644.93
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	67287*	204.11	131.97	13 734 058.32
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	32622*	150.88	80.40	4 921 996.03
May - Aug 2005	Total database	Number of medicine items/prescription	609044*	2.27	1.39	1384 135
	Cardiovascular items	Number of cardiovascular items/prescription	104445*	1.41	0.70	147 608
	Antihypertensive items	Number of antihypertensive items/prescription	76914*	1.20	0.47	92 620
	ACE inhibitors	Number of ACE inhibitors/prescription	37453*	1.00	0.07	37 622
	Total Database	Cost/prescription (R)	609044*	243.70	396.39	148 423 312.00
		Cost/ medicine item (R)	1384135	107.23	222.57	148 423 312.00
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	104445*	229.84	168.76	24 005 835.07
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	76914*	202.55	133.60	15 578 761.56
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	37453*	151.72	81.71	5 682 300.91

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1 (continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitor items from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Sep - Dec 2005	**Total database**	Number of medicine items/prescription	494766*	2.22	1.37	1 098 222
	Cardiovascular items	Number of cardiovascular items/prescription	97443*	1.43	0.71	139 049
	Antihypertensive items	Number of antihypertensive items/prescription	72153*	1.21	0.47	87 377
	ACE inhibitors	Number of ACE inhibitors/prescription	35042*	1.00	0.06	35 186
	Total database	Cost/prescription (R)	494766*	263.13	438.46	130 188 773.00
		Cost/ medicine item (R)	1098222	118.55	248.86	130 188 773.00
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	97443*	231.61	165.05	22 569 012.95
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	72153*	202.32	130.95	14 597 683.91
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	35042*	150.95	79.43	5 289 593.32

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1(continued): **Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitor items from 2001-2006**

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Jan - Apr 2006	**Total database**	Number of medicine items/prescription	329487*	2.36	1.43	778 669
	Cardiovascular items	Number of cardiovascular items/prescription	51155*	1.40	0.69	71 819
	Antihypertensive items	Number of antihypertensive items/prescription	38538*	1.23	0.49	47 473
	ACE inhibitors	Number of ACE inhibitors/prescription	17700*	1.00	0.07	17 780
	Total	Cost/prescription (R)	329487*	276.87	421.55	91 226 251.18
	Database	Cost of all medicine items (R)	778669	117.16	227.74	91 226 251.18
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	51155*	260.67	185.74	13 334 516.03
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	38538*	233.91	145.63	9 014 517.71
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	17700*	176.59	78.42	3 125 643.34
May - Aug 2006	**Total database**	Number of medicine items/prescription	348210*	2.40	1.44	834 501
	Cardiovascular items	Number of cardiovascular items/prescription	54376*	1.41	0.69	76 411
	Antihypertensive items	Number of antihypertensive items/prescription	41421*	1.24	0.50	51 227
	ACE inhibitors	Number of ACE inhibitors/prescription	18838*	1.00	0.06	18 914
	Total	Cost/prescription (R)	348210*	271.06	420.86	94 386 321.55
	Database	Cost of all medicine items (R)	834501	113.11	229.16	94 386 321.55
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	54376*	259.44	184.48	14 107 326.87
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	41421*	231.67	142.41	9 596 106.28
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	18838*	168.90	70.08	3 181 674.08

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1 (continued): Frequency and cost of all cardiovascular, antihypertensive and ACE inhibitor items from 2001-2006

Year	Description		Frequency (N)	Average	Standard deviation(±)	Total**
Sep - Dec 2006	Total database	Number of medicine items/prescription	319090*	2.37	1.45	757402
	Cardiovascular items	Number of cardiovascular items/prescription	54053*	1.42	0.70	76 882
	Antihypertensive items	Number of antihypertensive items/prescription	41785*	1.25	0.51	52 160
	ACE inhibitors	Number of ACE inhibitors/prescription	19129*	1.00	0.07	19 216
	Total database	Cost/prescription (R)	319090*	293.17	460.82	93 548 259.48
		Cost of all medicine items (R)	757402	123.51	256.44	93 548 259.48
	Cardiovascular	Cost/prescription containing cardiovascular item(s) (R)	54053*	267.01	188.37	14 432 949.43
	Antihypertensive	Cost/prescription containing antihypertensive item(s) (R)	41785*	237.07	146.59	9 906 129.95
	ACE inhibitors	Cost/prescription containing ACE inhibitor(s) (R)	19129*	169.64	69.60	3 245 108.34

* Number of prescriptions

** Total number of medicine items or total cost of medicine items as applicable

Table 5.1.1: The total number of cardiovascular, antihypertensive and ACE inhibitor prescriptions and medicine items as percentage of all prescriptions and items for year 2001-2006(%)

Period	Cardiovascular Items		Antihypertensive items		ACE inhibitor items	
	Prescriptions	Items	Prescriptions	items	Prescriptions	items
2001-2002	15.54%* (n=551851)	10.82%* (n=756847)	10.89%* (n=386820)	6.48%* (n=452873)	5.57%* (n=197771)	2.80%* (n=195937)
2004	19.85%* (n=515255)	13.68%* (n=725778)	14.36%* (n=372563)	8.32%* (n=441613)	7.05%* (n=182970)	3.47%* (n=184018)
2005	18.11%* (n=293694)	11.52%* (n=415559)	13.34%* (n=216354)	7.22%* (n=260376)	6.48%* (n=105117)	2.93%* (n=105571)
2006	16.00%* (n=159584)	9.50%* (n=225112)	12.21%* (n=121721)	6.36%* (n=150821)	5.59%* (n=55667)	2.36%* (n=55910)

*%= Number of cardiovascular/antihypertensive or ACE inhibitor prescriptions or items as applicable
Total number of prescriptions or medicine items as applicable

According to table 5.1.1 the contribution of prescriptions containing cardiovascular items to the total number of prescriptions claimed through the medicine claims database decreased by 1.74% (n=221561) from 2004 until 2005 and then decreased again by 2.11% (n=134110) from 2005 until 2006. Furthermore, the contribution of cardiovascular items to the total number items claimed decreased by 2.16% (n=310219) from 2004 until 2005 and then decreased by 2.02% (n=190447) from 2005 until 2006.

As shown in table 5.1.1 the total contribution made by prescriptions containing antihypertensive items showed a decrease of 1.02% (n=156209) from 2004 to 2005 and a further decrease of 1.13% (n=94633) from 2005 until 2006. The number of antihypertensive items decreased from 1.10% (n=181237) from 2004 until 2005 and then decreased again by 0.86% (n=109555) from 2005 until 2006.

Table 5.1.1 further shows that the contribution by the total number of ACE inhibitor containing prescriptions showed a continuous decrease by 0.57% (n=77853) from 2004 until 2005 and then a decrease by 0.89% (n=49450) from 2005 until 2006. The total number of ACE inhibitor items claimed through the database showed a decrease of 0.54% (n=78447) from 2004 until 2005 and then a larger decrease of 0.57% (n=49661) from 2005 until 2006.

It can therefore be concluded from table 5.1.1 that the contributions made by the cardiovascular, antihypertensive and ACE inhibitor items decreased from 2004 until 2006.

Furthermore, it can be seen from table 5.1 that the total number of prescriptions and the total number of medicine items claimed through the database also showed a decrease from 2004 until 2006.

The fact that there was a reduction in the total number of prescriptions from 2004 to 2005 might be due to the reduction in the number of medical schemes from 80 in 2004 to 68 in 2005 and a further reduction to 35 medical schemes in 2006. This reduction might be attributed to the possible reduction in medical scheme members, as well as a decrease in the number of prescriptions and medicine items claimed. The reasons(s) for reduction in the number of medical schemes as well as the possible reduction in medical scheme members falls outside the scope of this study and is therefore uncontrollable.

Table 5.1.2: The total number of cardiovascular, antihypertensive and ACE inhibitor prescriptions and medicine items as percentage of all prescriptions and items for Jan-Apr 2004-2006(%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Prescriptions	items	Prescriptions	items	Prescriptions	items
Jan-Apr 2004	20.36%* (n=145232)	14.92%* (n=203413)	14.62%* (n=104335)	9.08%* (n=123763)	7.02%* (n=50107)	3.69%* (n=50360)
Jan-Apr 2005	17.73%* (n=91806)	11.46%* (n=128902)	12.99%* (n=67287)	7.15%* (n=80379)	6.30%* (n=32622)	2.91%* (n=32763)
Jan-Apr 2006	15.53%* (n=51155)	9.22%* (n=71819)	11.70%* (n=38538)	6.10%* (n=47473)	5.37%* (n=17700)	2.28%* (n=17780)

*%= Number of cardiovascular/antihypertensive or ACE inhibitor prescriptions or items as applicable
Total number of prescriptions or medicine items as applicable

Table 5.1.2 shows that the contribution of prescriptions containing cardiovascular items to the total number of prescriptions claimed through the medical scheme administrator decreased by 2.63% (n=53426) and 2.20% (n=40651) from Jan-Apr 2004 until Jan-Apr 2005 and Jan-Apr 2005 until Jan-Apr 2006 respectively. The percentage of cardiovascular items represented from the total number of medicine items claimed decreased by 3.46% (n=74511) from Jan-Apr 2004 until Jan-Apr 2005 and decreased further by 2.24% (n=57083) from Jan-Apr 2005 until Jan-Apr 2006.

Furthermore, the percentage of prescriptions containing antihypertensive items represented from the total number of prescriptions claimed showed a decrease of 1.63% (n=37048) from

Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 0.93% (n=14922) from Jan-Apr 2005 until Jan-Apr 2006. The contribution made by the total number of antihypertensive items to the total number of medicine items claimed through the database showed a decrease of 1.93% (n=43384) from 2004 until 2005 and then a further decrease of 1.05% (n=32906) from 2005 until 2006.

According to table 5.1.2 the contribution made by the prescriptions containing ACE inhibitors to the total number of prescriptions claimed decreased by 0.72% (n=17485) from Jan-Apr 2004 until Jan-Apr 2005 and further decreased by 0.63% (n=14983) from Jan-Apr 2005 until Jan-Apr 2006.

It can be concluded that the percentage contributions made by the cardiovascular, antihypertensive and ACE inhibitor items and prescriptions decreased continuously from January-April 2004 until January-April 2006. Furthermore, as shown in table 5.1 the total number of items and prescriptions from the total database also decreased continuously for these periods. This might be due to the reduction in the number of medical schemes as well as the reduction in the number of medical scheme members.

Table 5.1.3: The total number of cardiovascular, antihypertensive and ACE inhibitor prescriptions and medicine items as percentage of all prescriptions and items for May-Aug 2004-2006(%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Prescriptions	items	Prescriptions	items	Prescriptions	items
May-Aug 2004	18.26%* (n=170917)	12.27%* (n=239798)	15.51%* (n=123486)	7.49%* (n=146293)	6.45%* (n=60328)	3.10%* (n=60661)
May-Aug 2005	17.15%* (n=104445)	10.66%* (n=147608)	12.63%* (n=76914)	6.69%* (n=92620)	6.15%* (n=37453)	2.72%* (n=37622)
May-Aug 2006	15.62%* (n=54376)	9.16%* (n=76411)	11.90%* (n=41421)	6.14%* (n=51227)	5.41%* (n=18838)	2.27%* (n=18914)

*%= Number of cardiovascular/antihypertensive or ACE inhibitor prescriptions or items as applicable
Total number of prescriptions or medicine items as applicable

According to table 5.1.3 the contribution made by prescriptions containing cardiovascular items as well as the total number of cardiovascular items to the total number of prescriptions and items claimed decreased by 1.11% (n=66472) and 1.61% (n=92190) respectively from May-August 2004 until May-August 2005. Cardiovascular containing prescriptions and

cardiovascular items further decreased by 1.53% (n=50069) and 1.50% (n=71197) respectively from May-August 2005 until May-August 2006.

The percentage that prescriptions containing antihypertensive items and cardiovascular items represented from the total number of prescriptions and the total number of items decreased of 2.88% (n=46572) and 0.80% (n=53673) respectively from May-August 2004 until May-August 2005. The period of May-August 2005 until May-August 2006 showed further decreases in the contributions in the number of antihypertensive prescriptions and antihypertensive items and further decreased by 0.73% (n=35493) and 0.55% (n=41393) respectively from May-August 2005 until May-August 2006.

The results in table 5.1.3 show that the percentage of prescriptions that containing ACE inhibitors decreased by 0.30% (n=22875) and the contribution made by the total number of ACE inhibitors to the total number of items from the database decreased by 0.38% (n=23039) for May-August 2004 until May-August 2005. The percentage ACE inhibitor containing prescriptions and the number of ACE inhibitor items decreased by 0.74% (n=18615) and 0.45% (n=18708) respectively from May-August 2005 until May-August 2006.

It can be concluded that the percentage contributions made by the cardiovascular, antihypertensive and ACE inhibitor items and prescriptions decreased continuously from May-August 2004 until May-August 2006. Furthermore, as shown in table 5.1 the total number of items and prescriptions from the total database also decreased continuously for these periods. This might be due to the reduction in the number of medical schemes as well as the reduction in the number of medical scheme members.

Table 5.1.4: The total number of cardiovascular, antihypertensive and ACE inhibitor prescriptions and medicine items as percentage of all prescriptions and items for Sept-Dec 2004-2006(%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Prescriptions	items	Prescriptions	items	Prescriptions	items
Sept-Dec 2004	21.04%* (n=199106)	14.21%* (n=282567)	15.30%* (n=144742)	8.63%* (n=171557)	7.67%* (n=72535)	3.67%* (n=72997)
Sept-Dec 2005	19.69%* (n=97443)	12.66%* (n=139049)	14.58%* (n=72153)	7.96%* (n=87377)	7.08%* (n=35042)	3.20%* (n=35186)
Sept-Dec 2006	16.94%* (n=54053)	10.15%* (n=76882)	13.10%* (n=41785)	6.89%* (n=52160)	5.99%* (n=19129)	2.54%* (n=19216)

*%= Number of cardiovascular/antihypertensive or ACE inhibitor prescriptions or items as applicable
Total number of all prescriptions or medicine items as applicable

As shown in table 5.1.4 the contribution made by prescriptions containing cardiovascular items decreased by 1.35% (n=101663) and the contribution made by the total number of cardiovascular items to the total number of items decreased from the database decreased by 1.55% (n=143518) from 2004 until 2005. The period of 2005 until 2006 showed a further decrease of 2.75% (n=43390) in the prevalence percentage of cardiovascular containing prescriptions as well as a reduction in the prevalence percentage of cardiovascular items of 1.09% (n=15913).

Table 5.1.4 further showed that the percentage represented by prescriptions containing antihypertensive items decreased by 0.72% (n=72589) and the percentage represented by the antihypertensive items decreased by 0.47% (n=84180) from Sept-Dec 2004 until Sept-Dec 2005. During the period of Sept-Dec 2005 until Sept-Dec 2006 the contributions of both the number of prescriptions containing antihypertensive items and the total number of antihypertensive items further decreased by 1.48% (n=30368) and 1.07% (n=35217) respectively.

It can be concluded that the percentage contributions made by the cardiovascular, antihypertensive and ACE inhibitor items and prescriptions decreased continuously from May-August 2004 until May-August 2006. Furthermore, as shown in table 5.1 the total number of items and prescriptions from the total database also decreased continuously for these periods.

In addition to this September-December 2004 showed the highest number of prescriptions containing cardiovascular, antihypertensive and ACE inhibitor items as well as the highest number of cardiovascular, antihypertensive and ACE inhibitor items claimed with regard to any of the other study periods. This might be attributed to the "full implementation" of the single exit price (refer to chapter 3, section 3.4.2.3).

5.1.1.2 Total cost and average cost per prescription

5.1.1.2.1. Introduction

The total cost and average cost per prescription of the cardiovascular, antihypertensive and ACE inhibitor items are summarised in table 5.1. This section will also include the cost percentage of cardiovascular, antihypertensive and ACE inhibitor items as part of the total cost of all medicine items claimed and will be discussed and summarised in table 5.1.5 to 5.1.8. The effect sizes (d-values) calculated between the different average cost per prescription are discussed and summarised in table 5.1.9.

Table 5.1.5: Total cost of cardiovascular, antihypertensive and ACE inhibitor items as percentage of the total cost of all medication items claimed for 2001-2006 (%)

Period	Cardiovascular Items	Antihypertensive items	ACE inhibitor items
2001-2002	17.55%* (n=R172 210 489.00)	9.96%* (n=R97 677 845.31)	4.07%* (n=R39 938 139.63)
2004	19.36%* (n=R128 023 228.00)	12.33%* (n=R81 520 365.83)	4.40%* (n=R29 100 326.90)
2005	16.70%* (n=R67 791 492.95)	10.82%* (n=R43 910 503.79)	3.92%* (n=R15 893 890.26)
2006	15.00%* (n=R41 874 792.33)	10.21%* (n=R28 508 628.11)	3.42%* (n=R9 552 425.76)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor items as applicable
Total cost of all medicine items

According to table 5.1.5 the contribution cardiovascular items made to the total cost of all medicine items claimed decreased by 2.66% (R60 231 735.05) from 2004 until 2005 and further decreased by 1.70% (R25 916 700.62) from 2005 until 2006.

The contribution antihypertensive items made to the total cost of all medicine items decreased by 1.51% (R37 609 862.04) from 2004 until 2005 and then decreased further by 0.61% (R15 401 875.68) from 2005 until 2006.

The contribution of ACE inhibitors to the total cost of all medicine items also decreased by 0.48% (R13 206 436.64) from 2004 until 2005 and then decreased further by 0.50% (R6 341 464.50) from 2005 until 2006.

It can therefore be concluded that the cost percentage of cardiovascular, antihypertensive and ACE inhibitor items showed a continuous decrease from 2004 until 2006. This might be due to the decrease in the number of prescriptions claimed from the database (refer to table 5.1.1) as well as a reduction in the average cost per item (refer to table 5.1).

Table 5.1.6: Total cost of cardiovascular, antihypertensive and ACE inhibitor items as percentage of the total cost of all medication items claimed for Jan-Apr 2004-2006 (%)

Period	Cardiovascular items	Antihypertensive items	ACE inhibitor items
Jan-Apr 2004	21.09%* (n=R41 950 474.27)	13.43%* (n=R26 718 220.57)	4.73%* (n=R9 404 465.25)
Jan-Apr 2005	16.68%* (n=R21 216 644.93)	10.80%* (n=R13 734 058.32)	3.87%* (n=R4 921 996.03)
Jan-Apr 2006	14.62%* (n=R13 334 516.03)	9.88%* (n=R9 014 517.71)	3.43%* (n=R3 125 643.34)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor items as applicable
Total cost of all medicine items

According to table 5.1.6 the contribution that cardiovascular items made to the total cost of all medicine items claimed showed a decrease of 4.41% (R20 733 829.34) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 2.06% (R7 882 128.90) from Jan-Apr 2005 until Jan-Apr 2006.

The contribution that antihypertensive items made to the total cost of all medicine items showed a decrease of 2.63% (R12 984 162.25) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 0.92% (R4 719 540.61) from Jan-Apr 2005 until Jan-Apr 2006.

Furthermore, the cost percentage of ACE inhibitors also showed a decrease of 0.86% (R4 482 469.22) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 0.44% (R1 796 352.69) from 2005 until 2006.

Table 5.1.7: Total cost of cardiovascular, antihypertensive and ACE inhibitor items as percentage of the total cost of all medication items claimed for May-Aug 2004-2006 (%)

Period	Cardiovascular items	Antihypertensive items	ACE inhibitor items
May-Aug 2004	18.02%* (n=R43 738 731.52)	11.48%* (n=R27 858 238.13)	4.07%* (n=R9 870 673.88)
May-Aug 2005	16.17%* (n=R24 005 835.07)	10.50%* (n=R15 578 761.56)	3.83%* (n=R5 682 300.91)
May-Aug 2006	14.95%* (n=R14 107 326.87)	10.12%* (n=R9 596 106.28)	3.37%* (n=R3 181 674.08)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor items as applicable
Total cost of all medicine items

As shown in table 5.1.7, the contribution the cardiovascular items made to the total cost of all medicine items claimed decreased by 1.85% (R19 732 896.45) from May-Aug 2004 until May-Aug 2005 and decreased further by 1.22% (R9 898 508.20) from May-Aug 2005 until May-Aug 2006.

The cost percentage of antihypertensive items decreased by 0.98% (R12 279 476.57) from May-Aug 2004 until May-Aug 2005 and decreased further by 0.38% (R5 982 655.28) from 2005 until 2006.

The contribution ACE inhibitors made to the total cost of all medicine items claimed decreased by 0.24% (R4 188 372.97) from May-Aug 2004 until May-Aug 2005, and the contribution decreased further by 0.46% (R2 500 626.83) from May-Aug 2005 until May-Aug 2006.

Table 5.1.8: Total cost of cardiovascular, antihypertensive and ACE inhibitor items as percentage of the total cost of all medication items claimed for Sept-Dec 2004-2006 (%)

Period	Cardiovascular items	Antihypertensive items	ACE inhibitor items
Sept-Dec 2004	19.28%* (n=R42 334 022.38)	12.27%* (n=R26 943 907.13)	4.47%* (n=R9 825 187.77)
Sept-Dec 2005	17.34%* (n=R22 569 012.95)	11.21%* (n=R14 597 683.91)	4.06%* (n=R5 289 593.32)
Sept-Dec 2006	15.43%* (n=R14 432 949.43)	10.59%* (n=R9 906 129.95)	3.47%* (n=R3 245 108.34)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor prescriptions or items as applicable
Total cost of all medicine items

As indicated in table 5.1.8 the cost percentage of cardiovascular items decreased by 1.94% (R19 765 009.43) from Sept-Dec 2004 until Sept-Dec 2005 and further decreased by 1.91% (R8 136 063.52) from Sept-Dec 2005 until Sept-Dec 2006.

According to table 5.1.8 the contribution antihypertensive items made to the total cost of all medicine items claimed from the database decreased by 1.06% (R12 346 223.22) from Sept-Dec 2004 until Sept-Dec 2005 and decreased even further from Sept-Dec 2005 until Sept-Dec 2006 by 0.62% (R4 691 553.96).

The contribution ACE inhibitors made to the total cost of all medicine items claimed decreased by 0.41% (R4 535 594.45) from September-December 2004 until September-December 2005 and from September-December 2005 until September-December 2006 the contribution decreased further by 0.59% (R2 044 484.98).

The period of September-December 2004 also showed the lowest average cost per prescription (refer to table 5.1) of R212.62 ± R157.05, R186.15 ± R123.62 and R135.45 ± R74.89 respectively for prescriptions containing cardiovascular, antihypertensive and ACE inhibitor items. This might be due to the "full" implementation of the new pricing regulations (SEP) (refer to chapter 3, section 3.4).

Table 5.1.9: Effect sizes calculated between the average cost/prescription for cardiovascular, antihypertensive and ACE inhibitor items for the different study periods

Period	Cardiovascular items	Antihypertensive items	ACE inhibitor items
2001-2002 to 2004	0.09	0.11	0.46
2004 to 2005	0.10	0.11	0.09
2005 to 2006	0.17	0.22	0.25
Jan-Apr 2004 to Jan-Apr 2005	0.28	0.33	0.37
Jan-Apr 2005 to Jan-Apr 2006	0.16	0.20	0.32
May-Aug 2004 to May-Aug 2005	0.14	0.16	0.13
May-Aug 2005 to May-Aug 2006	0.16	0.20	0.21
Sept-Dec 2004 to Sept-Dec 2005	0.12	0.12	0.20
Sept-Dec 2005 to Sept-Dec 2006	0.19	0.24	0.24

It can be concluded from the results in table 5.1.9 that the effect sizes (d-values) calculated between the average cost per prescription for cardiovascular, antihypertensive or ACE inhibitors for the different study periods are not of any practical significance (also refer to chapter 4, section 4.8.2.5). The effect sizes between the average cost per prescription between 2001 and 2006 for cardiovascular, antihypertensive and ACE inhibitor items are also not of practical significance.

5.1.3 Prevalence and cost of the innovator and generic products from the total database with reference to cardiovascular, antihypertensive and ACE inhibitor items

5.1.3.1 Introduction

In this section the prevalence and cost of all innovator and generic medicine items claimed are discussed. This will be done in two subsections (5.1.3.2 and 5.1.3.3) which separate the data on a basis of cost and prevalence. The cost and prevalence are summarised in table 5.2 and the percentages regarding the prevalence are summarised in table 5.2.1 to 5.2.4 and the percentages regarding the cost are summarised in table 5.2.5 to 5.2.8.

Table 5.2: Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovators and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001-2002	Cardiovascular drugs	Innovators	605010	79.94	254.80	109.80	154 158 405.00
		Generics	151837	20.06	118.89	79.13	18 052 083.87
		Total	**756847**	**100.00**	**227.14**	**117.71**	**172 210 489.00**
	Antihypertensive drugs	Innovators	379693	83.64	233.79	85.66	88 767 198.80
		Generics	74283	16.36	123.13	61.73	9 146 625.00
		Total	**453976**	**100.00**	**215.68**	**91.85**	**97 913 823.80**
	ACE inhibitors	Innovators	151370	76.10	223.20	74.52	33 785 207.56
		Generics	47551	23.90	129.40	57.35	6 152 932.07
		Total	**198921**	**100.00**	**200.47**	**81.32**	**39 938 139.63**
	All innovator drugs in database		5063299	72.40	166.02	207.29	840 590 931.00
	All generic drugs in database		1930172	27.60	72.77	69.88	140 467 884.00
Year 2004	Cardiovascular drugs	Innovators	477362	65.77	213.97	100.66	102 143 303.00
		Generics	248416	34.23	104.18	68.57	25 879 925.17
		Total	**725778**	**100.00**	**176.39**	**104.82**	**128 023 228.00**
	Antihypertensive drugs	Innovators	327036	74.15	213.82	90.34	69 925 524.24
		Generics	113996	25.85	100.74	61.51	11 483 427.14
		Total	**441032**	**100.00**	**184.59**	**97.37**	**81 408 951.38**
	ACE inhibitors	Innovators	112285	61.02	199.74	82.76	22 427 821.33
		Generics	71733	38.98	93.02	49.15	6 672 505.57
		Total	**184018**	**100.00**	**158.14**	**88.48**	**29 100 326.90**
	All innovator drugs in database		3525282	66.44	155.80	270.06	549 255 136.00
	All generic drugs in database		1780564	33.56	62.88	74.29	111 965 864.00

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovator and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2005	Cardiovascular drugs	Innovators	259358	62.41	202.31	95.91	52 471 799.95
		Generics	156201	37.59	98.08	62.26	15 319 693.00
		Total	**415559**	**100.00**	**163.13**	**98.73**	**67 791 492.95**
	Antihypertensive drugs	Innovators	176873	68.01	199.56	85.30	35 297 037.68
		Generics	83189	31.99	102.87	58.79	8 557 645.61
		Total	**260062**	**100.00**	**168.63**	**89.93**	**43 854 683.29**
	ACE inhibitors	Innovators	58993	55.88	190.39	74.43	11 231 774.85
		Generics	46578	44.12	100.09	54.13	4 662 115.41
		Total	**105571**	**100.00**	**150.55**	**79.99**	**15 893 890.26**
	All innovator drugs in database		2330359	64.61	143.27	272.21	333 863 321.00
	All generic drugs in database		1276633	35.39	56.37	73.74	71 965 775.97
Year 2006	Cardiovascular drugs	Innovators	134280	59.65	234.06	105.43	31429057.94
		Generics	90832	40.35	115.00	65.76	10445734.390
		Total	**225112**	**100.00**	**186.02**	**108.57**	**41874792.33**
	Antihypertensive drugs	Innovators	94114	62.43	227.79	89.91	21438601.22
		Generics	56707	37.57	124.68	58.48	7070026.89
		Total	**150938**	**100.00**	**189.04**	**93.99**	**28533467.15**
	ACE inhibitors	Innovators	32315	57.80	200.28	67.28	6472026.21
		Generics	23595	42.20	130.55	56.15	3080399.55
		Total	**55910**	**100.00**	**170.85**	**71.64**	**9552425.76**
	All innovator drugs in database		1416011	59.73	152.04	294.67	21588806
	All generic drugs in database		954561	40.27	66.91	85.48	63872025.91

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovators and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Cardiovascular drugs	Innovators	140641	69.14	242.03	106.26	34 039 589.48
		Generics	62772	30.86	126.03	76.28	7 910 884.79
		Total	**203413**	**100.00**	**206.23**	**111.69**	**41 950 474.27**
	Antihypertensive drugs	Innovators	95394	77.19	243.85	94.93	23 261 877.03
		Generics	28193	22.81	121.17	66.53	3 416 277.06
		Total	**123587**	**100.00**	**215.87**	**103.03**	**26 678 154.09**
	ACE inhibitors	Innovators	32833	65.12	227.80	91.39	7 478 961.43
		Generics	17527	34.88	109.86	49.31	1 925 503.82
		Total	**50360**	**100.00**	**186.74**	**97.20**	**9 404 465.25**
	All innovator drugs in database		914922	67.10	178.04	336.26	162 890 319.00
	All generic drugs in database		448649	32.90	80.34	87.58	36 043 288.01
May - Aug 2004	Cardiovascular drugs	Innovators	159631	66.57	220.87	102.00	35 257 225.40
		Generics	80167	33.43	105.80	69.96	8 481 506.12
		Total	**239798**	**100.00**	**182.40**	**107.28**	**43 738 731.52**
	Antihypertensive drugs	Innovators	109796	75.14	220.19	90.18	24 176 071.81
		Generics	36318	24.86	100.32	62.61	3 643 374.04
		Total	**146114**	**100.00**	**190.40**	**98.84**	**27 819 445.85**
	ACE inhibitors	Innovators	37955	62.57	204.84	81.36	7 774 842.69
		Generics	22706	37.43	92.30	48.31	2 095 831.19
		Total	**60661**	**100.00**	**162.72**	**89.34**	**9 870 673.88**
	All innovator drugs in database		1310108	67.05	154.75	243.03	202 739 655.00
	All generic drugs in database		643725	32.95	62.11	73.45	39 981 055.63

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovator and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Cardiovascular drugs	Innovators	177090	62.67	185.48	86.54	32 846 488.12
		Generics	105477	37.33	89.95	58.33	9 487 534.26
		Total	**282567**	**100.00**	**149.82**	**89.99**	**42 334 022.38**
	Antihypertensive drugs	Innovators	121846	71.12	184.56	76.94	22 487 575.40
		Generics	49485	28.88	89.40	54.32	4 423 776.04
		Total	**171331**	**100.00**	**157.07**	**83.20**	**26 911 351.44**
	ACE inhibitors	Innovators	41497	56.85	172.88	67.08	7 174 017.21
		Generics	31500	43.15	84.16	47.21	2 651 170.56
		Total	**72997**	**100.00**	**134.60**	**73.83**	**9 825 187.77**
	All innovator drugs in database		1300252	65.39	141.22	241.05	183 625 163.00
	All generic drugs in database		688190	34.61	52.23	62.60	35 941 520.15

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovator and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Cardiovascular drugs	Innovators	84779	65.75	200.53	95.34	17 000 954.99
		Generics	44166	34.25	95.55	62.96	4 220 054.52
		Total	**128945**	**100.00**	**164.57**	**99.07**	**21 221 009.51**
	Antihypertensive drugs	Innovators	57886	72.02	198.38	83.62	11 483 295.37
		Generics	22493	27.98	100.07	59.19	2 250 762.95
		Total	**80379**	**100.00**	**170.87**	**89.24**	**13 754 058.32**
	ACE inhibitors	Innovators	19281	58.85	187.45	73.68	3 614 192.59
		Generics	13482	41.15	97.00	53.91	1 307 803.44
		Total	**32763**	**100.00**	**150.23**	**79.82**	**4 921 996.03**
	All innovator drugs in database		748718	66.57	143.26	245.94	107 259 034.00
	All generic drugs in database		375918	33.43	53.10	70.44	19 958 008.09
May - Aug 2005	Cardiovascular drugs	Innovators	92324	62.55	201.61	96.25	18 612 607.45
		Generics	55186	37.45	97.55	62.65	5 393 227.62
		Total	**147608**	**100.00**	**162.63**	**99.00**	**24 005 835.07**
	Antihypertensive drugs	Innovators	63307	68.44	198.59	85.96	12 571 852.17
		Generics	29198	31.56	102.34	59.60	2 988 139.52
		Total	**92505**	**100.00**	**168.21**	**90.44**	**15 559 991.69**
	ACE inhibitors	Innovators	21012	55.85	191.68	75.37	4 027 535.73
		Generics	16610	44.15	99.62	54.72	1 654 765.18
		Total	**37622**	**100.00**	**151.72**	**81.71**	**5 682 300.91**
	All innovator drugs in database		898198	64.89	135.86	266.53	122 024 950.00
	All generic drugs in database		485937	35.11	54.32	74.04	26 398 361.42

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovator and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Cardiovascular drugs	Innovators	82260	59.16	204.94	96.07	16 858 423.43
		Generics	56789	40.84	100.56	61.21	5 710 589.52
		Total	**139049**	**100.00**	**162.31**	**98.10**	**22 569 012.95**
	Antihypertensive drugs	Innovators	55778	63.91	201.87	86.32	11 259 842.43
		Generics	31495	36.09	105.37	57.65	3 318 557.22
		Total	**87273**	**100.00**	**167.04**	**90.05**	**14 578 399.65**
	ACE inhibitors	Innovators	18700	53.15	191.98	74.05	3 590 046.53
		Generics	16486	46.85	103.09	53.56	1 699 546.79
		Total	**35186**	**100.00**	**150.33**	**78.91**	**5 289 593.32**
	All innovator drugs in database		686990	62.55	152.76	304.03	104 947 135.00
	All generic drugs in database		411232	37.45	61.38	75.84	25 241 638.52

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovators and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2006	Cardiovascular drugs	Innovators	43177	60.12	233.30	104.98	10073359.83
		Generics	28642	39.88	113.86	67.12	3261156.2
		Total	**71819**	**100.00**	**185.67**	**108.82**	**13 334 516.03**
	Antihypertensive drugs	Innovators	29890	62.96	228.40	89.80	6826877.05
		Generics	17583	37.04	124.42	61.45	2187640.66
		Total	**47473**	**100.00**	**189.89**	**94.86**	**9 014 517.71**
	ACE inhibitors	Innovators	10234	57.56	209.36	71.97	2142553.98
		Generics	7546	42.44	130.28	59.55	983089.36
		Total	**17780**	**100.00**	**175.80**	**77.55**	**3 125 643.34**
	All innovator drugs in database		467826	60.08	152.48	280.60	71 334 129.81
	All generic drugs in database		310843	39.92	63.99	81.92	19 892 121.37
May - Aug 2006	Cardiovascular Drugs	Innovators	45399	59.41	232.36	104.97	10549029.17
		Generics	31012	40.59	114.74	64.76	3558297.70
		Total	**76411**	**100.00**	**184.62**	**107.64**	**14 107 326.87**
	Antihypertensive Drugs	Innovators	31894	62.26	225.58	88.58	7194745.63
		Generics	19333	37.74	124.21	56.26	2401360.65
		Total	**51227**	**100.00**	**187.33**	**92.17**	**9 596 106.28**
	ACE inhibitors	Innovators	10981	58.06	195.37	64.70	2145368.02
		Generics	7933	41.94	130.63	55.16	1306306.06
		Total	**18914**	**100.00**	**168.22**	**68.75**	**3 181 674.08**
	All innovator drugs in database		495661	59.40	145.10	285.16	71 919 587.77
	All generic drugs in database		338840	40.60	66.30	81.83	22 466 733.78

Table 5.2 (continued): Cost and prevalence of cardiovascular, antihypertensive and ACE inhibitor innovator and generic items for 2001-2006

Year	Description		Frequency (N)	Frequency %	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Cardiovascular drugs	Innovators	45704	59.45	236.45	106.26	10806668.94
		Generics	31178	40.55	116.31	65.46	3626280.49
		Total	**76882**	**100.00**	**187.73**	**109.22**	**14 432 949.43**
	Antihypertensive drugs	Innovators	32369	62.06	229.39	91.32	7425104.37
		Generics	19791	37.94	125.36	57.88	2481025.58
		Total	**52160**	**100.00**	**189.92**	**94.84**	**9 906 129.95**
	ACE inhibitors	Innovators	11100	57.76	196.77	64.43	2184104.21
		Generics	8116	42.24	130.73	53.79	1061004.13
		Total	**19216**	**100.00**	**168.88**	**68.44**	**3 245 108.34**
	All innovator drugs in database		452588	59.77	159.11	318.01	72 011 612.27
	All generic drugs in database		304688	40.23	70.60	92.58	21 511 039.98

5.1.3.2 Prevalence of innovator and generic products in total database

As shown in table 5.2 the prevalence percentage of cardiovascular innovators decreased by 14.17% (n=127648) from 2001 until 2004 and therefore showed an increase of 14.14% in prevalence percentage of cardiovascular generics. The prevalence percentage further decreased by 3.36% (n=218004) from 2004 until 2005 and then decreased by 2.76% (n=125078) from 2005 until 2006. The prevalence percentage of antihypertensive innovators also decreased by 9.49% (n=52657) from 2001 until 2004. The prevalence percentage of the antihypertensive innovators further decreased by 6.14% (n=150163) from 2004 until 2005 and then further decreased by 5.58% (n=82759) from 2005 until 2006. The prevalence percentage of the ACE inhibitor innovators decreased by 15.08% (n=39085) from 2001 until 2004 and then decreased further by 5.14% (n=53292) from 2004 until 2005. The prevalence percentage of the ACE inhibitor innovators then increased by 1.92% while the number of items decreased by 26678 from 2005 until 2006. The decrease in innovators lead to an increase in generic use, which might be attributed to the fact that the pharmacist should inform the public on the advantages of generic substitution as of 2003.

In this section the innovator and generic cardiovascular, antihypertensive and ACE inhibitor items as part of the total prevalence of innovator and generic items are discussed and summarised in table 5.2.1 to 5.2.4.

Table 5.2.1: Prevalence percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for 2001-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
2001-2002	11.95%* (n=605010)	7.87%* (n=151837)	7.50%* (n=379693)	3.85%* (n=74283)	2.99%* (n=151370)	2.46%* (n=47551)
2004	13.54%* (n=477362)	13.95%* (n=248416)	9.28%* (n=327036)	6.40%* (n=113996)	3.19%* (n=112285)	4.03%* (n=71733)
2005	11.13%* (n=259358)	12.24%* (n=156201)	7.59%* (n=176873)	6.52%* (n=83189)	2.53%* (n=58993)	3.65%* (n=46578)
2006	9.48%* (n=134280)	9.52%* (n=90832)	6.65%* (n=97114)	5.94%* (n=56707)	2.28%* (n=32315)	2.47%* (n=23595)

*%= Total prevalence of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable
Total prevalence of innovator or generic medicine items as applicable

According to table 5.2.1 the contribution made by the cardiovascular innovator items to the total prevalence of all innovator items claimed decreased by 2.41% (n=218004) from 2004 until 2005 and decreased further by 1.65% (n=125078) from 2005 until 2006. The contribution made by the cardiovascular generics to the total prevalence of all generic items claimed decreased by 1.69% (n=92215) from 2004 until 2005 and decreased even further by 2.72% (n=65369) from 2005 until 2006.

Antihypertensive innovator items represented 7.50% of all innovator items during 2001-2002 and decreased by 1.69% (n=150163) from 2004 until 2005 and decreased further from 2005 until 2006 of 0.94% (n=79759). The prevalence percentage of generic antihypertensive items increased by 0.12% from 2004 until 2005 and decreased by 0.58% (n=26482) from 2005 until 2006.

Table 5.2.1 reveals that the prevalence percentage of ACE inhibitor innovators decreased by 0.66% (n=53292) from 2004 until 2005 and decreased further by 0.25% (n=26678) from 2005 until 2006. The contribution made by the ACE inhibitor generics showed a decrease of 0.38% (n=25155) from 2004 until 2005 and a further decrease of 1.18% (n=22983) from 2005 until 2006.

According to table 5.2.1 the period of 2001-2002 showed that the contribution made by innovators were consistently higher than that of generics, this might be attributed to the fact that generic substitution was made compulsory by law in 2003 (refer to chapter 2, section 2.4.5).

It can be concluded from 5.1.3.2 that the prevalence percentage made by generic items were higher than that of innovators from 2004 until 2006 for cardiovascular and ACE inhibitor items. The number of innovator items was consistently higher than that of generic items. In contrast to this the contributions from the antihypertensive innovators were consistently higher from 2004 until 2006.

Table 5.2.2: Prevalence percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for Jan-Apr 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
Jan-Apr 2004	15.37%* (n=140641)	13.99%* (n=62772)	10.43%* (n=95394)	6.28%* (n=28193)	3.59%* (n=32833)	3.91%* (n=17527)
Jan-Apr 2005	11.32%* (n=84779)	11.75%* (n=44166)	7.73%* (n=57886)	5.98%* (n=22493)	2.58%* (n=19281)	3.59%* (n=13482)
Jan-Apr 2006	9.23%* (n=43177)	9.21%* (n=28642)	6.39%* (n=29890)	5.66%* (n=17583)	2.19%* (n=10234)	2.43%* (n=7546)

*%= Total prevalence of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable
Total prevalence of innovator or generic medicine items as applicable

As shown in table 5.2.2 the contribution made by the cardiovascular innovator items decreased consistently by 4.05% (n=55862) from Jan-Apr 2004 until Jan-Apr 2005 and 2.09% (n=41602) from Jan-Apr 2005 until Jan-Apr 2006. The cardiovascular generic items showed a decrease in contribution of 2.24% (n=18606) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 2.54% (n=15524) from Jan-Apr 2005 until Jan-Apr 2006.

Antihypertensive innovator items showed a decrease in contribution of 2.70% (n=37508) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 1.34% (n=27996) from Jan-Apr 2005 until Jan-Apr 2006. The antihypertensive generic items showed a decrease in the contribution of 0.30% (n=5700) and a further decrease of 0.32% (n=4910) from Jan-Apr 2005 until Jan-Apr 2006.

According to table 5.2.2 the contribution of the ACE inhibitor innovator items decreased by 1.01% (n=13552) from Jan-Apr 2004 until Jan-Apr 2005 and decreased by 0.39% (n=9047) from Jan-Apr 2005 until Jan-Apr 2006.

It can therefore be concluded that the contribution of the ACE inhibitor innovator items to all innovator items was consistently higher than the contribution ACE inhibitor generics made to the all generic items as well as for the cardiovascular items in January-April 2005. All the other items showed a larger contribution made by the innovator items.

Table 5.2.3: Prevalence percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for May-Aug 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
May-Aug 2004	12.19%* (n=159631)	12.45%* (n=80176)	17.06%* (n=109796)	5.64%* (n=36318)	2.90%* (n=37955)	3.53%* (n=22706)
May-Aug 2005	10.28%* (n=92324)	11.36%* (n=55186)	7.05%* (n=63307)	6.01%* (n=29198)	2.34%* (n=21012)	3.42%* (n=16610)
May-Aug 2006	9.16%* (n=45399)	9.15%* (n=31012)	6.44%* (n=31894)	5.71%* (n=19333)	2.22%* (n=10981)	2.34%* (n=7933)

*%= Total prevalence of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable
Total prevalence of innovator or generic medicine items as applicable

According to table 5.2.3 the contribution made by the cardiovascular innovator items decreased by 1.91% (n=67307) from 2004 until 2005 and decreased further by 1.12% (n=46925) from 2005 until 2006. The cardiovascular generic items decreased by 1.09% (n=24990) from 2004 until 2005 and decreased even further by 2.21% (n=24174) from 2005 until 2006.

As shown in table 5.2.3 the contribution made by antihypertensive innovator items decreased by 10.01% (n=46489) from 2004 until 2005 and a further decrease of 0.61% (n=31413) from 2005 until 2006. The generic antihypertensive items showed an increase of 0.37% even though the number of items decreased by 7120 from 2004 until 2005.

Table 5.2.3 reveals that the contribution made by ACE inhibitor innovator items showed a decrease of 0.56% (n=16943) from 2004 until 2005 and a further decrease of 0.12% (n=10031) from 2005 until 2006. The ACE inhibitor innovator items showed a decrease of 0.11% (n=6095) from 2004 until 2005 and a further reduction of 1.08% (n=8677) from 2005 until 2006. The contribution of generic ACE inhibitor items decreased by 0.11% (n=6095) form 2004 until 2005 and decreased even further by 1.08% (n=8677) from 2005 until 2006.

It can therefore be concluded that ACE inhibitors as well as cardiovascular items consistently showed a higher contribution by the generic items than by the innovator items in the period May-August 2006. All the other items showed larger contributions made by the innovator items.

Table 5.2.4: Prevalence percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for Sept-Dec 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
Sept-Dec 2004	13.62%* (n=177090)	15.33%* (n=105477)	9.37%* (n=121846)	7.19%* (n=49485)	3.19%* (n=41497)	4.58%* (n=31500)
Sept-Dec 2005	11.97%* (n=55778)	13.81%* (n=56789)	8.12%* (n=55778)	7.66%* (n=31495)	2.72%* (n=18700)	4.01%* (n=16486)
Sept-Dec 2006	10.10%* (n=45704)	10.23%* (n=31178)	7.15%* (n=32369)	6.50%* (n=19791)	2.45%* (n=11100)	2.66%* (n=8116)

*%= Total prevalence of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable
Total prevalence of innovator or generic medicine items as applicable

As shown in table 5.2.4 the contribution made by cardiovascular innovator items showed a decrease of 1.65% (n=121312) from 2004 until 2005 and a further decrease of 1.87% (n=10074) from 2005 until 2006. The cardiovascular innovator items decreased by 1.52%

(n=48688) from 2004 until 2005 and a further decrease of 3.58% (n=25611) was experienced during 2005 until 2006.

The contribution antihypertensive innovator items made to the total prevalence of all innovator items decreased by 1.25% (n=66068) from 2004 until 2005 and decreased further by 0.97% (n=23409) from 2005 until 2006. Antihypertensive generic items increased by 0.47% even though the number of items decreased by 17990.

According to table 5.2.4 the contribution the ACE inhibitor innovator items made to the total prevalence of all the innovator items decreased by 0.47% (n=22797) from 2004 until 2005 and decreased further by 0.27% (n=7600) from 2005 until 2006. The contribution ACE inhibitor generic items made to the total prevalence of all generic items claimed from the database decreased by 0.57% (n=15014) from 2004 until 2005 and the contribution decreased further by 1.35% (n=8370) from 2005 until 2006.

5.1.3.3 Total cost and average cost of all innovators and generics from the total database

All data used in this section were extracted from table 5.2. The total cost of the cardiovascular, antihypertensive and ACE inhibitor items as part of the total cost of all innovator and generic items is summarised in table 5.2.5 to 5.2.8 and the average cost per item is discussed and summarised in table 5.2.9

Table 5.2.5: Cost percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for 2001-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
2001-2002	18.34%* (n=R154 158 405.00)	12.85%* (n=R18 052 083.87)	10.56%* (n=R88 767 198.80)	6.51%* (n=R9 146 625.00)	3.44%* (n=R33 785 207.56)	4.38%* (n=R6 152 932.07)
2004	18.60%* (n=R102 143 303.00)	23.11%* (n=R25 879 925.17)	12.73%* (n=R69 925 524.24)	10.26%* (n=R11 483 427.14)	4.08%* (n=R22 427 821.33)	5.60%* (n=R6 672 505.57)
2005	15.72%* (n=R52 471 799.95)	21.29%* (n=R15 319 693.00)	10.57%* (n=R35 297 037.68)	11.89%* (n=R8 557 645.61)	3.36%* (n=R11 231 774.85)	6.48%* (n=R4 662 115.41)
2006	14.60%* (n=R31 429 057.94)	16.35%* (n=R10 445 734.39)	9.96%* (n=R21 438 601.22)	11.07%* (n=R7 070 026.89)	3.01%* (n=R6 472 026.21)	4.82%* (n=R3 080 399.55)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable

Total cost of innovator or generic medicine items as applicable

Table 5.2.6: Cost percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for Jan-Apr 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
Jan-Apr 2004	20.90%* (n=R34 039 589.48)	21.95%* (n=R7 910 884.79)	14.28%* (n=R23 261 877.03)	9.48%* (n=R3 416 277.06)	4.59%* (n=R7 478 961.43)	5.34%* (n=R1 925 503.82)
Jan-Apr 2005	15.85%* (n=R17 000 954.99))	21.14%* (n=R4 220 054.52)	10.71%* (n=R11 483 295.37))	11.28%* (n=R2 250 762.37)	3.37%* (n=R3 614 192.59)	6.55%* (n=R1 307 803.44)
Jan-Apr 2006	14.12%* (n=R10 073 359.83)	16.39%* (n=R3 261 156.20)	9.57%* (n=R6 826 877.05)	11.00%* (n=R2 187 640.66)	3.00%* (n=R2 142 553.98)	4.94%* (n=R983 089.36)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable

Total cost of innovator or generic medicine items as applicable

According to table 5.2.5 the contribution made by the cardiovascular innovator items to the total cost of all innovator items decreased by 2.88% (n=R49 671 503.05) from 2004 until 2005 and decreased even more by 1.12% (n=R21 042 742.01) from 2005 until 2006. The contribution by the cardiovascular generic items to the total cost of generic items decreased by 1.82% (n=R10 560 232.17) from 2004 until 2005 and decreased further by 4.94% (n=R487 395 861.00) from 2005 until 2006.

The contribution of antihypertensive innovator items to the total cost of all innovator items showed a decrease of 2.16% (n=R3 462 886.56) from 2004 until 2005 and a further decrease of 0.61% (n=R13 858 436.46) from 2005 until 2006. The contribution of the antihypertensive generic items increased by 1.63% although the total cost of all the generic items decreased by R34 628 486.56 from 2004 until 2005. The total cost of the generic items decreased from 2005 until 2006 by 0.82% (n=R148 761 872.00).

Table 5.2.5 reveals that the contribution ACE inhibitor innovator items made to the total cost of all the innovator items decreased by 0.72% (R11 196 046.48) from 2004 until 2005 and decreased further by 0.35% (n=R4 759 748.64) from 2005 until 2006. The contribution of the ACE inhibitor generic items increased by 0.88% although the total cost decreased by R2 010 390.16 from 2005 until 2006.

According to table 5.2.6 the contribution the cardiovascular innovator items made to the total cost of all innovator items decreased by 5.05% (n=R17 038 634.49) from Jan-Apr 2004 until Jan-Apr 2005 and decreased even further by 1.73% (n=R6 927 595.16) from Jan-Apr 2005 until Jan-Apr 2006. The contribution by the cardiovascular generic items showed a decrease of 0.81% (n=R3 690 830.27) from Jan-Apr 2004 until Jan-Apr 2005 and a further decrease of 4.75% (n=R958 898.32) from Jan-Apr 2005 until Jan-Apr 2006.

Furthermore, table 5.2.6 shows that the contribution the antihypertensive innovator items made to the total cost of all innovator items decreased by 3.57% (n=R11 778 581.66) from Jan-Apr 2004 until Jan-Apr 2005 and then showed a decrease of 1.14% from 2005 until 2006 and the total cost of the generic antihypertensive items increased by 1.80% from Jan-Apr 2004 until Jan-Apr 2005 and Jan-Apr 2005 until Jan-Apr 2006 showed a decrease of 0.28% (n=R63 121.71).

The contribution the ACE inhibitor innovator items made to the total cost of all innovator items decreased by 1.22% (n=R3 864 768.84) from Jan-Apr 2004 until Jan-Apr 2005 and then decreased further by 0.37% (n=R1 471 638.61) from Jan-Apr 2005 until Jan-Apr 2006. The ACE inhibitor generic items however showed an increase in contribution of 1.21%, although the total cost of the ACE inhibitor generic items decreased by R617 700.38 from Jan-Apr 2004 until Jan-

Apr 2005 and then decreased again by 1.61% (n=R324 714.08) from Jan-Apr 2005 until Jan-Apr 2006.

Table 5.2.7: Cost percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for May-Aug 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
May-Aug 2004	17.39% (n=R35 257 225.40)	21.21% (n=R8 481 506.12)	11.92% (n=R24 176 071.81)	9.11% (n=R3 643 374.04)	3.83% (n=R7 774 842.69)	5.24% (n=R2 095 831.19)
May-Aug 2005	15.25% (n=R18 612 607.45)	20.43% (n=R5 393 227.62)	10.30% (n=R12 571 852.17)	11.32% (n=R2 988 139.52)	3.30% (n=R4 027 535.73)	6.27% (n=R1 654 765.18)
May-Aug 2006	14.67% (n=R10 549 029.17)	15.84% (n=R3 558 297.70)	10.00% (n=R7 194 745.63)	10.69% (n=R2 401 360.65)	2.98% (n=R2 145 368.02)	5.81% (n=R1 306 306.06)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable

Total cost of innovator or generic medicine items as applicable

Table 5.2.8: Cost percentage of cardiovascular, antihypertensive and ACE inhibitors according to innovator and generic status for Sept-Dec 2004-2006 (%)

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator items	Generic items	Innovator items	Generic items	Innovator items	Generic items
Sept-Dec 2004	17.89% (n=R32 846 488.12)	26.40% (n=R9 487 534.26)	12.25% (n=R22 487 575.40)	12.31% (n=R4 423 776.04)	3.91% (n=R7 174 017.21)	7.38% (n=R2 651 170.56)
Sept-Dec 2005	16.06% (n=R16 858 423.43)	22.62% (n=R5 710 589.52)	10.73% (n=R11 259 842.43)	13.15% (n=R3 318 557.22)	3.42% (n=R3 590 046.53)	6.73% (n=R1 699 546.79)
Sept-Dec 2006	15.01% (n=R10 806 668.94)	16.86% (n=R3 626 280.49)	10.31% (n=R7 425 104.37)	11.53% (n=R2 481 025.58)	3.03% (n=R2 184 104.21)	4.93% (n=R1 061 004.13)

*%= Total cost of cardiovascular/antihypertensive or ACE inhibitor innovator or generic medicine items as applicable

Total cost of innovator or generic medicine items as applicable

According to table 5.2.7 the contribution the cardiovascular innovator items made to the total cost of all the innovator items decreased by 2.14% (n=R35 257 206.79) from 2004 until 2005 and decreased further by 0.58% (n=R806 378.28) from 2005 until 2006. The cardiovascular generic items showed a decrease of 0.78% (n=R3 088 278.50) from 2004 until 2005 and a further decrease of 4.59% (n=R1 834 929.92) from 2005 until 2006.

Table 5.2.7 further shows that the contribution of antihypertensive innovator items decreased by 1.62% (n=R11 604 219.64) from 2004 until 2005 and then showed an increase of 0.30% (n=R5 377 106.54) from 2005 until 2006. Furthermore, the contribution of the generic cardiovascular items increased by 2.21%, although the total cost of the antihypertensive generic items decreased by R655 234.52. The period from 2005 until 2006 showed a decrease of 0.63% (n=R837 531.64).

The contribution the ACE inhibitor innovator items made to the total cost of all innovator items showed a decrease of 0.53% (n=R3 747 306.96) from 2004 until 2005 and a further decrease of 0.32% (n=R1 882 167.71) from 2005 until 2006. In addition to this the contribution of the ACE inhibitor generic items increased by 1.03% although the total cost decreased by R441 066.01 from 2004 until 2005. Furthermore, the contribution of ACE inhibitor generics decreased by 0.46% (n=R348 459.12) from 2005 until 2006.

As shown in table 5.2.8 the contribution made by cardiovascular innovator items decreased by 1.83% (n=R15 988 064.69) from 2004 until 2005 and decreased further by 1.05% (n=R6 051 754.49) from 2005 until 2006. The contribution made by cardiovascular innovator items showed a decrease of 3.78% (n=R15 988 064.69) from 2004 until 2005 and a further decrease of 5.76% (n=R2 084 309.03) from 2005 until 2006.

Table 5.2.8 further showed the contribution made by antihypertensive innovator items decreased by 1.52% (n=R11 227 732.97) from 2004 until 2005 and decreased further by 0.42% (n=R3 834 738.06) from 2005 until 2006. The antihypertensive generic items increased by 1.62% although the total cost decreased by R1 105 218.82 from 2004 until 2005 and a further decrease of 1.62% (n=R837 531.64) from 2005 until 2006.

The contribution ACE inhibitor innovator items made to the total cost of all innovator items showed a decrease of 0.65% (n=R951 623.77) from 2004 until 2005 and a further decrease of 0.39% (n=R1 405 942.32) from 2005 until 2006. In addition to this the contribution of ACE inhibitor generic items decreased by 0.65% (n=R951 623.77) from 2004 until 2005. Furthermore, the contribution of ACE inhibitor generics decreased by 1.80% (n=R638 542.66) from 2005 until 2006.

It can therefore be concluded that the generic cardiovascular, antihypertensive and ACE inhibitor items showed larger overall contributions to the total cost of all the generic medicine

items than the contributions made by the cardiovascular, antihypertensive and ACE inhibitor innovator items to the total cost of all the innovators items from the database.

Table 5.2.9: Average cost per cardiovascular, antihypertensive and ACE inhibitor item according to innovator and generic status for the four monthly study periods for 2004-2006

Period	Cardiovascular items		Antihypertensive items		ACE inhibitor items	
	Innovator	Generic	Innovator	Generic	Innovator	Generic
Jan-Apr 2004	R242.03 ± R 106.26	R126.03 ± R 76.28	R243.85 ± R 94.93	R121.17 ± R 66.53	R227.80 ± R 91.39	R109.86 ± R 49.31
May-Aug 2004	R220.03 ± R 102.00	R105.80 ± R 69.96	R220.19 ± R 90.18	R100.32 ± R 62.61	R204.84 ± R 81.36	R92.30 ± R 48.31
Sept-Dec 2004	R185.48± R 86.54	R89.95± R 58.33	R184.56 ± R 76.94	R89.40 ± R 54.32	R172.88 ± R 67.08	R84.16 ± R 47.21
Jan-Apr 2005	R200.53± R 95.34	R95.55± R 62.96	R198.38 ± R 83.62	R100.07 ± R 59.19	R187.45 ± R 73.68	R97.00 ± R 53.91
May-Aug 2005	R201.61± R 96.25	R97.55± R 62.65	R198.59 ± R 85.96	R102.34 ± R 59.60	R 191.68 R 75.37	R99.62 ± R 54.72
Sept-Dec 2005	R204.94± R 96.07	R100.56± R 61.21	R201.87 ± R 86.32	R105.37 ± R 57.65	R191.98 ± R 74.05	R103.09 ± R 53.56
Jan-Apr 2006	R233.30± R 104.98	R113.86± R 67.12	R228.40 ± R 89.80	R124.42 ± R 61.45	R 209.36 ± R 71.97	R 130.28 ± R 59.55
May-Aug 2006	R232.36± R 104.97	R114.74± R 64.76	R225.58 ± R 88.58	R124.21 ± R 56.26	R 195.37 ± R 64.70	R 130.63 ± R 55.16
Sept-Dec 2006	R236.45± R 106.26	R116.31± R 65.46	R229.39 ± R 91.32	R125.36 ± R 57.88	R 196.77 ± R 64.43	R 130.73 ± R 53.79

As shown in table 5.2.9 the average cost per item for both innovator and generic items decreased continuously from January-April 2004 to September-December 2004, where this period also showed the lowest average cost per item for the entire study period of 2004 until 2006. This might be attributed to the "full" implementation of the pricing regulations (refer to chapter 3, section 3.4.2.3). The fact that the price did not decrease even more might be due to the pricing regulations being set aside by the Constitutional Court in December 2004 (refer to chapter 3, section 3.4.2.4). The average cost therefore stayed relatively constant throughout 2005, but the pricing regulations were declared invalid in September 2005 and showed an increase in average cost per item in January-April 2006. Throughout 2006 the average cost per item then remained relatively constant. Although the average cost per item decreased and increased throughout 2004-2006, the average cost of the antihypertensive and ACE inhibitor generics ended higher in Sept-Dec 2006 than it was at the beginning of 2004.

From table 5.2.9 it can further be seen that the average cost per item for cardiovascular innovators showed an overall increase of 0.16% from January 2004 until December 2006, the

cardiovascular generics had a reduction of 4.28% for the same time period. The antihypertensive innovators showed a reduction of 3.04% and the generics an increase of 7.84% from January 2004 until December 2006. The average cost per item of the ACE inhibitor innovators decreased by 11.74% and the generics increased by 23.37% from January 2004 until December 2006.

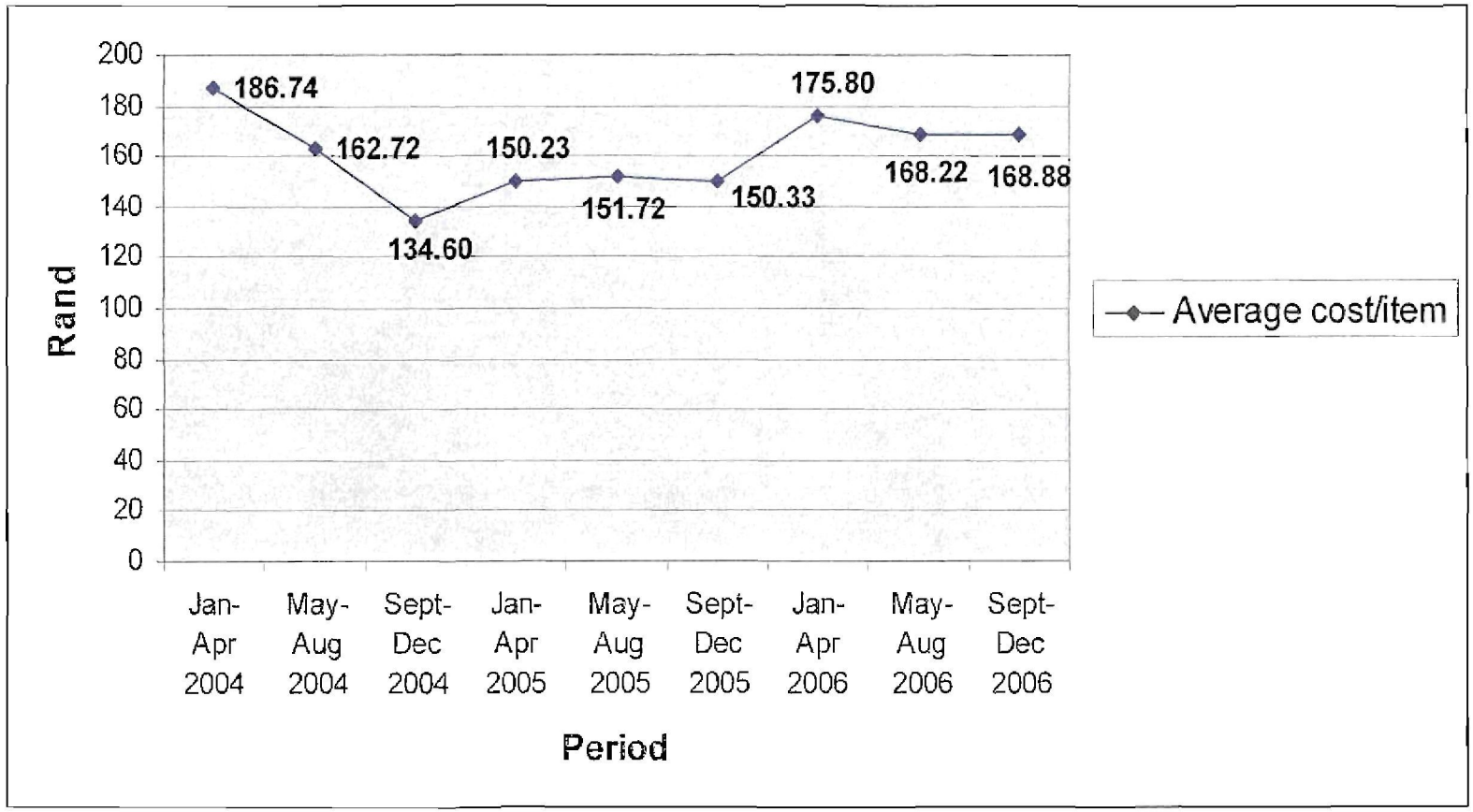

Figure 5.2: Average cost per ACE inhibitor item from 2004 until 2006

Note that the standard deviation is not shown in figure 5.2.

Figure 5.2, shows the average cost per ACE inhibitor item from 2004 until 2006. On 2 August 2004 the "full" implementation of the pricing regulations was experienced and thus showed the lowest average cost per item (standard deviation not shown). Then on 20 December 2004 the Constitutional court set the regulations aside and pharmacists could ask their "own dispensing fee", which resulted in an increase in average cost during Jan-April 2005.

In September 2005 the regulations were declared invalid (doctors and pharmacists could now ask their own fee to cover the cost of dispensing), which led to an increase in the average cost per item during Jan-April 2006. The price in Sept-Dec 2006 leveled off and was lower than before the regulations were implemented. Even though the average cost per ACE inhibitor item increased and decreased during 2004 to 2006, the overall average cost per ACE inhibitor item decreased by 5.43%.

It can also be seen that the implementation of the pricing regulations during 2004 had a definite impact on the average cost per ACE inhibitor item as illustrated in figure 5.2.

It can be concluded that although the average cost per medicine item of all of the medicine classes described above experienced increases and decreases throughout 2004 until 2006 with regard to the medicine pricing regulations, all of the classes except the antihypertensive generics and ACE inhibitor generics showed decreases in the average cost per medicine item.

5.1.3.3.1 Savings of all medicine item costs with regard to single exit price

5.1.3.3.1.1 Introduction

In this section the expected cost savings from the implementation of the single exit price on all medicine items will be applied to cardiovascular, antihypertensive items and ACE inhibitors to determine whether these expected savings occurred. The "↓" in table 5.2.10.1 indicates the estimated savings percentage, and the "↑" indicates the estimated cost percentage increase and therefore no cost savings. The estimated expected cost percentages in table 5.2.10.2 were calculated from the average cost per item in table 5.2.10.1.

All of the percentages in table 5.2.10.2 were calculated by determining the percentage increase or decrease in average cost per item by comparing all of the individual study periods during 2004 until 2006 with Jan 2004-Apr 2004 which was used as the basis year. This period (Jan 2004-Apr 2004) was the period before there was any implementation of the pricing regulations.

Table 5.2.10.1: Average cost of cardiovascular, antihypertensive and ACE inhibitor items for four monthly periods for 2004-2006

Description		Jan-Apr 2004	May-Aug 2004	Sept-Dec 2004	Jan-Apr 2005	May-Aug 2005	Sept-Dec 2005	Jan-Apr 2006	May-Aug 2006	Sept-Dec 2006
Innovator items	Cardiovascular items	R 242.03	R 220.87	R 185.48	R 200.53	R 201.61	R 204.94	R233.30	R 232.36	R 236.45
	Antihypertensive items	R 243.85	R 220.19	R 184.56	R 198.38	R 198.59	R 201.87	R 228.40	R 225.58	R 229.39
	ACE inhibitor items	R 227.80	R 204.84	R 172.88	R 187.45	R 191.68	R 167.04	R 209.36	R 195.37	R 196.77
Generic items	Cardiovascular items	R 126.03	R 105.80	R 89.95	R 95.55	R 97.55	R 100.56	R 113.86	R 114.74	R 116.31
	Antihypertensive items	R 121.17	R 100.32	R 89.40	R 100.07	R 102.34	R 105.37	R 124.42	R 124.21	R 125.36
	ACE inhibitor items	R 109.86	R 92.30	R 84.16	R 97.00	R 99.62	R 103.09	R 130.28	R 130.63	R 130.73
Total items	Cardiovascular items	R 206.23	R 182.40	R 149.82	R 164.57	R 162.63	R 162.31	R 185.67	R 184.62	R 187.73
	Antihypertensive items	R 215.87	R 190.40	R 157.07	R 170.87	R 168.21	R 167.04	R 189.89	R 187.33	R 189.92
	ACE inhibitor items	R 186.74	R 162.72	R 134.60	R 150.23	R 151.72	R 150.33	R 175.80	R 168.22	R 168.88

Table 5.2.10.2: Estimated expected cost percentage changes with the implementation of the single exit price with Jan 2004-Apr 2004 as basis

Description		May-Aug 2004	Sept-Dec 2004	Jan-Apr 2005	May-Aug 2005	Sept-Dec 2005	Jan-Apr 2006	May-Aug 2006	Sept-Dec 2006
Innovator items	Cardiovascular items	↓8.70%	↓23.36%	↓17.15%	↓16.70%	↓15.32%	↓3.61%	↓4.00%	↓2.31%
	Antihypertensive items	↓9.70%	↓24.31%	↓18.65%	↓18.56%	↓17.22%	↓6.33%	↓7.49%	↓5.93%
	ACE inhibitor items	↓10.08%	↓24.11%	↓17.71%	↓15.86%	↓26.67%	↓8.09%	↓14.24%	↓13.62%
Generic items	Cardiovascular items	↓16.05%	↓28.63%	↓24.18%	↓22.60%	↓20.21%	↓9.66%	↓8.96%	↓7.71%
	Antihypertensive items	↓17.21%	↓26.22%	↓17.41%	↓15.54%	↓13.04%	↑2.68%	↑2.51%	↑3.46%
	ACE inhibitor items	↓15.98%	↓23.39%	↓11.71%	↓9.32%	↓6.16%	↑18.59%	↑18.91%	↑19.00%
Total items	Cardiovascular items	↓11.56%	↓27.35%	↓20.20%	↓21.14%	↓21.30%	↓9.97%	↓10.48%	↓8.97%
	Antihypertensive items	↓11.80%	↓27.24%	↓20.85%	↓22.08%	↓22.62%	↓12.04%	↓13.22%	↓12.02%
	ACE inhibitor items	↓12.86%	↓27.92%	↓19.55%	↓18.75%	↓19.50%	↓5.86%	↓9.92%	↓9.56%

Refer to chapter 3, section 3.4.2.5 for a review of the expected cost savings.

It can be concluded from table 5.2.10.2 that cardiovascular and antihypertensive innovator items showed the largest reduction in cost percentage during Sept 2004 - Dec 2004 of 23.36% and 24.31% respectively. This was except for ACE inhibitor innovators that showed the largest reduction in cost percentage of 26.67% during Sept 2005 - Dec 2005. These reductions during 2004 might be attributed to the "full" implementation of the pricing regulations, thus showing the lowest average cost per item (refer to table 5.2.10.1).

For the generic items the cost percentage of cardiovascular, antihypertensive and ACE inhibitor items showed the largest decrease of 28.63%, 26.22% and 23.39% respectively during Sept 2004 - Dec 2004. In addition to this only generic antihypertensive and ACE inhibitor items showed increases in cost percentage and that was throughout 2006, with the highest increase during Sept 2006 – Dec 2006. These increases might be attributed to the pricing regulations being declared invalid in September 2005 (refer to chapter 3, section 3.4.2.4).

Table 5.2.10.2 further revealed that the total cardiovascular, antihypertensive and ACE inhibitor items showed the highest reduction in cost percentage during September-December 2004 of 27.35%, 27.24% and 27.92% respectively. The total ACE inhibitor average cost per item decreased by 12.86% (R24.02) from Jan 2004 - Apr 2004 (phase before the pre-implementation phase of the pricing regulations) until May-August (pre implementation phase of the pricing regulations). After that the total ACE inhibitor average cost per item decreased by 27.92% (R52.14) from May - Aug 2004 (phase before the pre-implementation phase of the pricing regulations) until Sept 2004 - Dec 2004 ("full" implementation phase of the pricing regulations). This reduction in average cost per item showed the impact of the pre implementation as well as the "full" implementation phase of the pricing regulations.

It can be concluded that the reduction in the total cost percentage was lowest during the "full' implementation of the pricing regulations. Furthermore, all of the innovator items showed a higher than 15% reduction in average cost per item during Sept 2004-Dec 2005 (refer to chapter 3, section 3.4.2.5 for the expected savings). The total cost of cardiovascular ,antihypertensive and ACE inhibitor items decreased between 25% and 30% between Sept 2004-Dec 2004 as shown in table 5.2.10.2, and estimated by figure 3.3. These results however were only obtained from Interpharm® Datasystems and not from all the medicine claim databases in the private health care sector of South Africa.

5.2 Prevalence of ACE inhibitor active ingredients

- *Year 2001-2002*

The prevalence of all ACE inhibitor active ingredients is illustrated in figure 5.3, below. Also refer to appendix A, table A1.

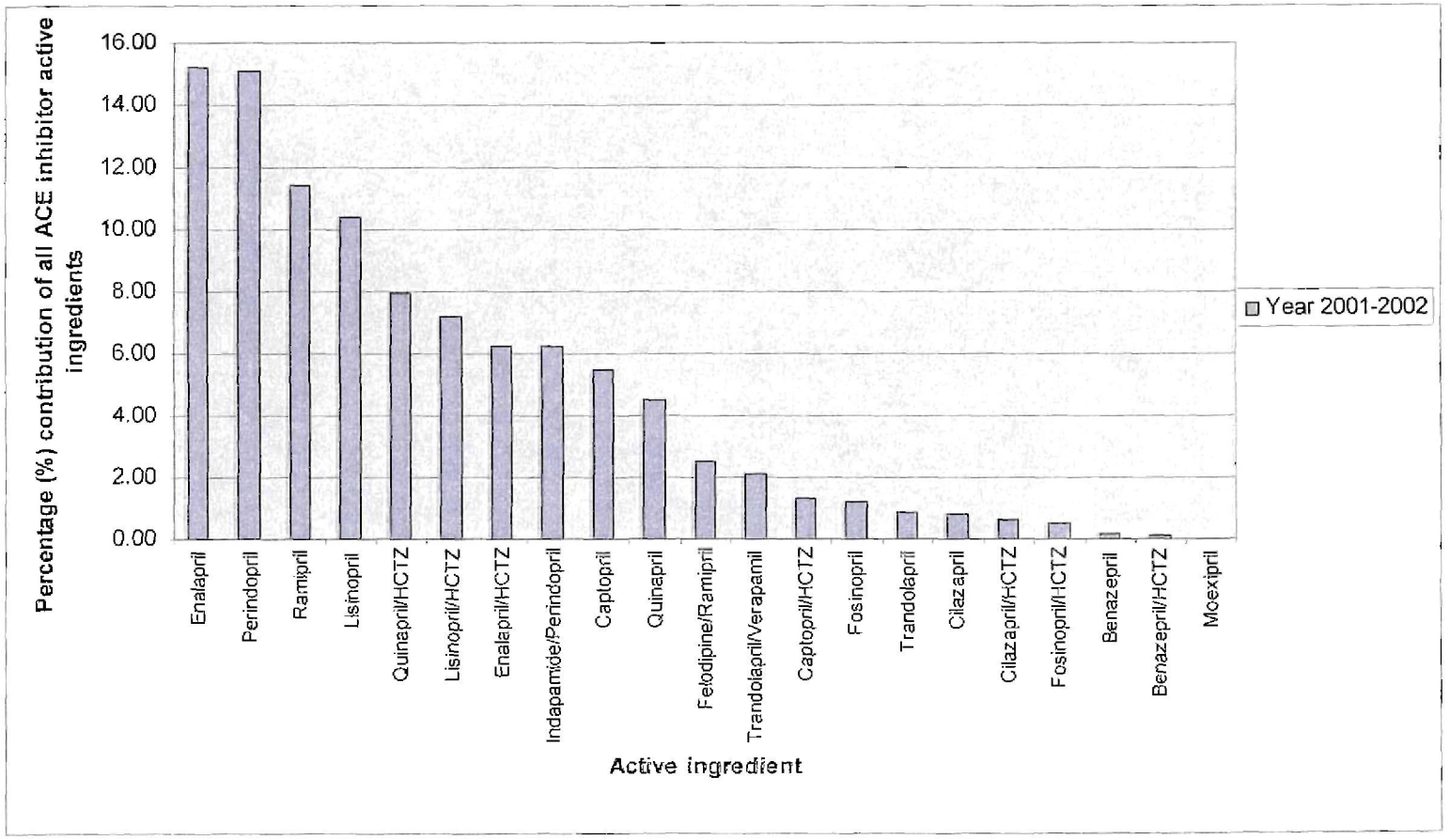

Figure 5.3: Prevalence of ACE inhibitor active ingredients for the period 2001-2002

From figure 5.3 and appendix A, table A1 it can be concluded that the active ingredient with the highest prevalence percentage during 2001-2002 (including single as well as combination medicine items) were enalapril (15.21%) followed by perindopril (15.10%). Furthermore, it can be seen that the top four items are all single items followed by four combination items. The two combination items with the highest prevalence percentage are quinapril/HCTZ (7.96%), followed by lisinopril/HCTZ (7.22%). The active ingredient with the lowest prevalence percentage is moexipril (0.00%) and the combination item with the lowest prevalence percentage comes from benazepril/HCTZ (0.14%).

In addition to this, figure 5.3 shows that the prevalence of the enalapril single items is more than double (15.21%) that of the enalapril combination (6.23%) (also refer to appendix A, table A1).

- *Year 2004 versus year 2005 versus year 2006*

According to figure 5.4 and appendix A, table A2 the active ingredient in **2004** with the highest prevalence percentage was perindopril with 18.34%, followed by the perindopril combination item with indapamide with 14.86% and enalapril with 14.32%. The item with the lowest prevalence percentage was ramipril/HCTZ.

In **2005** (refer to figure 5.4 and appendix A, table A3) items with the largest prevalence percentage were again perindopril and indapamide/perindopril. The prevalence percentage increased from 2004 until 2005 with 6.62% and 7.74% respectively, even though the number of items for both active ingredients decreased by 7397 and 3481 items respectively. The other two active ingredients which also showed increases in prevalence percentages from 2004 to 2005 were trandalopril/verapamil (0.39%) and moexipril (0.40%). Furthermore, perindopril and indapamide/perindopril together contributed to almost half of the prevalence percentage of all the active ingredients (47.56%) during 2005. In addition to this the only active ingredient prevalent in 2004 but not in 2005 was ramipril/HCTZ, possibly due to the fact that ramipril/HCTZ was no longer available on the market.

As shown in figure 5.4 and appendix A table A4 in **2006** the two active ingredients with the largest contribution were again perindopril and indapamide/perindopril. Both of these active ingredients showed a continuous increase in prevalence percentage from 2004 to 2006 with perindopril always having a larger prevalence percentage, but in 2006 indapamide/perindopril had the largest prevalence percentage, although the total number of items of both these active ingredients decreased. Perindopril showed an increase of 6.47% and indapamide/perindopril showed an increase of 13.63% with regard to the previous period, even though the number of items decreased by 8785 items and 3599 items respectively. These two items combined

contributed 67.66% of all ACE inhibitor active ingredients for 2006. Furthermore, as in 2005 ramipril/HCTZ was again not prevalent in 2006.

The other two active ingredients that showed continuous increases in prevalence percentages from 2004 to 2006 were trandalopril/verapamil and moexipril.

It can be concluded that trandolapril/verapamil, perindopril and indapamide/perindopril moexipril, showed increases in their prevalence percentages from 2004 until 2006. Perindopril and indapamide/perindopril were the only two active ingredients that consistently showed higher prevalence percentages than the other active ingredients. This showed the increasing and consistent, widespread use of these active ingredients (refer to appendix B, table B8 for the tradenames of the products containing perindopril and indapamide/perindopril).

The fact that some of the active ingredients showed decreases in prevalence percentages might be attributed to the reduction in the number of patients that received these items and/or the reduction in the number of prescriptions containing these items and/or the reduction in the number of medical aids and/or the reduction in the number of medical aid members (due to the reduction in the number of medical aids).

Navookarasu *et al.* (1999:28) stated that the increases in perindopril use in another study might be due to the fact that in heart failure the first-dose hypotensive effects are not appreciably higher than that of the placebo and are significantly fewer than those observed with captopril, enalapril and lisinopril, even in elderly patients with heart failure. Although heart failure was not investigated specifically in this study, this shows some of the advantages of using perindopril over other ACE inhibitors in general.

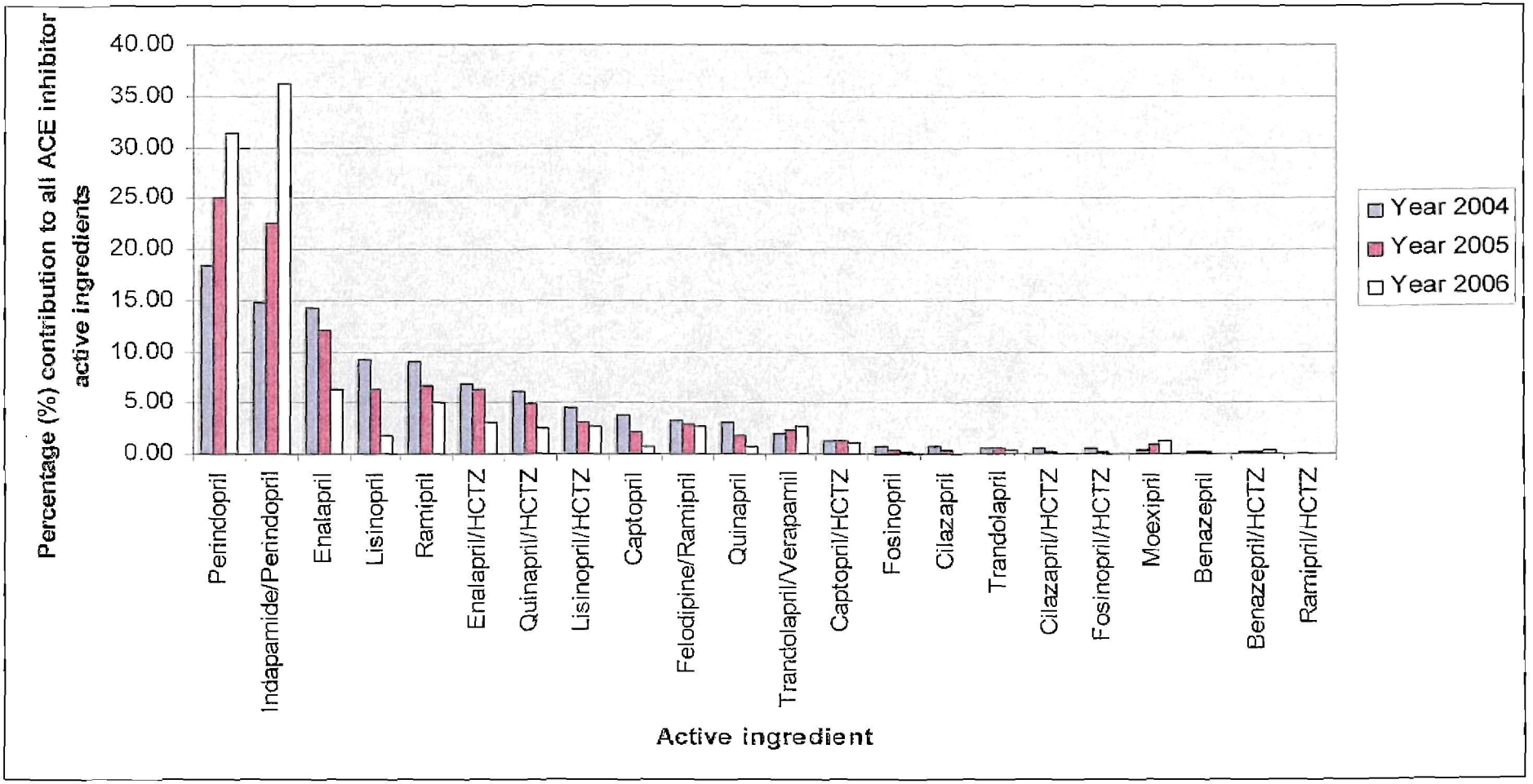

Figure 5.4: Prevalence of ACE inhibitor active ingredients for the year 2004, 2005 and 2006

5.3 ACE inhibitors as percentage of cardiovascular drugs

5.3.1 Introduction

In this section the total number of ACE inhibitors as percentage of the total number of cardiovascular items claimed is discussed and illustrated in table 5.2.11-5.2.14.

Table 5.2.11: Prevalence percentage of ACE inhibitors as percentage of all cardiovascular items for 2001-2006 (%)

Period	Prevalence
2001-2002	26.28%* (n=198921)
2004	25.35%* (n=184018)
2005	25.40%* (n=105571)
2006	24.84%* (n=55910)

*%= Total prevalence of all ACE inhibitor medicine items / Total prevalence of all cardiovascular medicine items

According to table 5.2.11 the contribution ACE inhibitors made to the total prevalence of all cardiovascular items showed an increase of 0.05% (n=78447) from 2004 until 2005 and a decrease of 0.56% (n=49661) from 2005 until 2006. The prevalence percentage stayed relatively stable between 26.28% to 24.84% from 2004 until 2006.

Table 5.2.12: Prevalence percentage of ACE inhibitors as percentage of all cardiovascular items for Jan-Apr 2004-2006 (%)

Period	Prevalence
Jan-Apr 2004	24.76%* (n=60360)
Jan-Apr 2005	25.41%* (n=32763)
Jan-Apr 2006	24.76%* (n=17780)

*%= Total prevalence of all ACE inhibitor medicine items / Total prevalence of all cardiovascular medicine items

It can be concluded from table 5.2.12 that the prevalence percentage of ACE inhibitors of cardiovascular items increased by 0.65% from Jan-Apr 2004 until Jan-Apr 2005. The number of

items in the same period decreased by 27 597 items. The period from Jan-Apr 2005 until Jan-Apr 2006 showed a decrease in the prevalence percentage of 0.65% as well as a decrease of 14983 in the total number of items.

Table 5.2.13: Prevalence percentage of ACE inhibitors as percentage of all cardiovascular items for May-Aug 2004-2006 (%)

Period	Prevalence
May-Aug 2004	25.30%* (n=239798)
May-Aug 2005	25.49%* (n=37622)
May-Aug 2006	24.75%* (n=18914)

*%= Total prevalence of all ACE inhibitor medicine items / Total prevalence of all cardiovascular medicine items

According to table 5.2.13 the prevalence percentage that ACE inhibitors represented showed an increase 0.19% but a decrease of 202176 items. The period of May-Aug 2005 until May-Aug 2006 also showed a decrease in the prevalence percentage of 0.74% as well as a decrease in the number of items of 18708.

Table 5.2.14: Prevalence percentage of ACE inhibitors as percentage of all cardiovascular items for Sept-Dec 2004-2006 (%)

Period	Prevalence
Sept-Dec 2004	25.83%* (n=72997)
Sept-Dec 2005	25.31%* (n=35186)
Sept-Dec 2006	24.99%* (n=19216)

*%= Total prevalence of all ACE inhibitor medicine items / Total prevalence of all cardiovascular medicine items

Table 5.2.14 shows that the contribution ACE inhibitors made to the total prevalence of all the cardiovascular items showed a continuous decrease from Sept 2004-Dec 2004 until Sept 2006-Dec 2006. The percentage decreased by 0.52% (n=37811) from Sept 2004-Dec 2004 until Sept 2005-Dec 2005 and a further decrease of 0.32% (n=15970) from Sept 2005-Dec 2005 until Sept 2006-Dec 2006.

It can be concluded that the January to April period and the May to August period showed the same pattern where the percentage contribution increased from 2004 until 2005 and then decreased from 2005 until 2006. September-December 2004 until September-December 2006 however showed a continuous decrease.

The highest percentage contribution made by the ACE inhibitors was during September – December 2004 and the smallest percentage contribution was made during May-August 2006.

5.4 ACE inhibitors as part of antihypertensive drugs

5.4.1 Introduction

During this section the total number of ACE inhibitors which form part of the total number of antihypertensive items claimed will be analysed from this database with regard to prevalence.

Table 5.2.15: Prevalence percentage of ACE inhibitors as percentage of antihypertensive items for 2001-2006

Period	Prevalence
2001-2002	43.82%* (n=198921)
2004	41.72%* (n=184018)
2005	40.59%* (n=105571)
2006	37.04%* (n=55910)

*%= Total prevalence of all ACE inhibitor medicine items / Total prevalence of all antihypertensive medicine items

According to table 5.2.15 the contribution that ACE inhibitors made showed a continuous decrease from 2004 until 2006. The contribution decreased by 1.13% (n=78447) from 2004 until 2005 and 3.55% (n=49661) from 2005 until 2006.

Table 5.2.16: Prevalence percentage of ACE inhibitors as percentage of antihypertensive items for Jan-Apr 2004-2006

Period	Prevalence
Jan-Apr 2004	40.75%* (n=60360)
Jan-Apr 2005	40.76%* (n=32763)
Jan-Apr 2006	37.45%* (n=17780)

*%= Total prevalence of all ACE inhibitor medicine items
Total prevalence of all antihypertensive medicine items

As shown in table 5.2.16 the contribution made by ACE inhibitors to the prevalence of antihypertensive items showed an increase of 0.01% (n=27597) from Jan-Apr 2004 to Jan-Apr 2005 and a decrease of 3.31% (n=14983) from Jan-Apr 2005 until Jan-Apr 2006. Although the prevalence percentage from Jan-Apr 2004 until Jan-Apr 2005 increased, the number of ACE inhibitor items decreased which therefore means that the number of antihypertensive items also decreased. This might be due to the total number of prescriptions and items that decreased from 2004 until 2005.

Table 5.2.17: Prevalence percentage of ACE inhibitors as percentage of antihypertensive items for May-Aug 2004-2006

Period	Prevalence
May-Aug 2004	41.52%* (n=60661)
May-Aug 2005	40.67%* (n=37622)
May-Aug 2006	36.92%* (n=18914)

*%= Total prevalence of all ACE inhibitor medicine items
Total prevalence of all antihypertensive medicine items

Table 5.2.17 shows that there was a decrease throughout these periods. The contribution decreased by 0.85% (n=23039) from May-Aug 2004 until May-Aug 2005 and a larger decrease of 3.75% (n=18708) from 2005 until 2006.

Table 5.2.18: Prevalence percentage of ACE inhibitors as percentage of antihypertensive items for Sept-Dec 2004-2006

Period	Prevalence
Sept-Dec 2004	42.61%* (n=72997)
Sept-Dec 2005	40.32%* (n=35186)
Sept-Dec 2006	36.84%* (n=19216)

*%= Total prevalence of all ACE inhibitor items / Total prevalence of all antihypertensive items

Table 5.2.18 also shows a constant decrease in the contribution made by the ACE inhibitors to the total antihypertensive prevalence. The period 2004 until 2005 showed a decrease of 2.29% (n=37811) and 2005 until 2006 showed a larger decrease of 3.48% (n=15970).

It can therefore be concluded that September-December 2004 showed the largest contribution made by ACE inhibitors as a percentage of antihypertensive items. This shows the same pattern in the contribution made by ACE inhibitors to cardiovascular items. September-December 2006 showed the smallest contribution of ACE inhibitors to all antihypertensive items. This might be due to the full implementation of the pricing regulations and therefore then showed the lowest average cost per ACE inhibitor item which led to an increase in prevalence.

5.5 Cost analysis of the top 20 ACE inhibitors

5.5.1 Introduction

In this section the top 20 ACE inhibitors are listed in tables 5.3, 5.4, 5.5 and 5.6 as well as the top 5 ACE inhibitors in table 5.7 according to prevalence for the period 2001-2002, 2004, 2005 and 2006. These ACE inhibitors will be discussed regarding prevalence, total cost and cost-prevalence index (CPI).

- *Year 2001-2002*

Table 5.3: Prevalence and cost of the top 20 ACE inhibitor items according to prevalence for 2001-2002

Position	Tradename	Frequency (N)	Frequency %*	Total cost (R)	Total cost %@	CPI#
1	Coversyl® 4mg	30031	15.10	6 528 300.76	16.35	1.09
2	Coversyl Plus®	12378	6.22	2 995 329.77	7.50	1.21
3	Zestoretic® 20/12.5mg	9023	4.54	2 599 389.49	6.51	1.43
4	Accuretic® 20/12.5mg	8865	4.46	2 137 571.22	5.35	1.20
5	Tritace® 5mg	8584	4.32	2 443 548.44	6.12	1.42
6	Co-Rentiec®	8295	4.17	1 964 838.06	4.92	1.18
7	Tritace® 2.5mg	7351	3.70	1 412 379.40	3.54	0.96
8	Accuretic® 10/12.5mg	6974	3.51	1 105 207.15	2.77	0.79
9	Zetomax® 10mg	6588	3.31	740 811.72	1.85	0.56
10	Zetomax® 20mg	5797	2.91	1 051 656.73	2.63	0.90
11	Zestoretic® 10/12.5mg	5348	2.69	898 491.82	2.25	0.84
12	Renitec® 10mg	4837	2.43	695 413.54	1.74	0.72
13	Renitec® 20mg	4802	2.41	1 137 265.06	2.85	1.18
14	Accupril® 10mg	4375	2.20	713 836.37	1.79	0.81
15	Tarka®	4160	2.09	1 328 582.54	3.33	1.59
16	Pharmapress Co®	3589	1.80	644 316.77	1.61	0.89
17	Pharmapress® 10mg	3448	1.73	381 989.73	0.96	0.55
18	HR-Enalapril® 10mg	3418	1.72	404 510.96	1.01	0.59
19	Pharmapress® 20mg	3400	1.71	600 094.20	1.50	0.88
20	Tritace® 10mg	3293	1.66	921 049.51	2.31	1.39

CPI (Cost Prevalence Index) refer to chapter 4, section 4.8.2.4.

*These percentages were calculated as percentage of the total prevalence of all ACE inhibitor items and not the total prevalence of the top 20 ACE inhibitor items.

@ These percentages were calculated as percentage of the total cost of all ACE inhibitor items and not the total cost of the top 20 ACE inhibitor items.

According to table 5.3, it can be seen that the ACE inhibitor product with the largest prevalence in 2001 - 2002 was Coversyl® with 30 031 prescription items, followed by combination agent namely Coversyl Plus®. The product with the highest total cost was Coversyl® and contributed 21.26% (n=R6 528 300.76) of the total cost (N=R30 704 583.24) of the top 20 ACE inhibitor products. The lowest total cost (n=R381 989.73) came from Pharmapress® 10mg, which also had the lowest CPI of 0.55 (refer to chapter 4, section 4.8.2.4). This indicates that this product was the most inexpensive of the top 20 products (also refer to chapter 4, section 4.8.2.4). The highest CPI came from Tarka® which had a CPI of 1.59, and this indicates that it was relatively expensive. Furthermore, it can be seen from table 5.3 that 45% (n=9) of the top 20 products had a CPI >1.

- *Year 2004*

Table 5.4: Prevalence and cost of the top 20 ACE inhibitor items according to prevalence for 2004

Position	Tradename	Frequency (N)	Frequency %*	Total cost (R)	Total cost %@	CPI#
1	Coversyl Plus®	25926	14.09	5 467 572.61	11.79	0.84
2	Prexum® 4mg	20959	11.39	2 875 557.50	9.88	0.87
3	Coversyl® 4mg	12793	6.95	2 148 208.06	7.38	1.06
4	Pharmapress Co®	6851	3.72	652 970.28	2.24	0.60
5	Accuretic® 20/12.5mg	6679	3.63	1 569 267.30	5.39	1.49
6	Zetomax® 20mg	5796	3.15	582 196.95	2.00	0.64
7	Zetomax® 10mg	5742	3.12	360 760.81	1.24	0.40
8	Pharmapress® 10mg	5586	3.04	265 711.35	0.91	0.30
9	Tritace® 5mg	5406	2.93	1 504 368.58	5.17	1.76
10	Zestoretic® 20/12.5mg	5406	2.93	1 354 353.45	4.65	1.58
11	Pharmapress® 20mg	5346	2.91	475 491.97	1.63	0.56
12	Co-Renitec®	4757	2.59	564 051.15	1.94	0.75
13	Tritace® 10mg	4520	2.46	1 290 207.88	4.43	1.81
14	Accuretic® 10/12.5mg	4470	2.43	718 683.64	2.47	1.02
15	Tritace® 2.5mg	4374	4.01	808 095.45	2.78	1.17
16	Tri-Plen Forte®	3681	2.00	1 169 569.31	4.02	2.01
17	Tarka®	3628	1.97	1 081 418.51	3.72	1.88
18	Zestoretic® 10/12.5mg	2976	1.61	1 354 353.45	4.65	2.88
19	Renitec® 20mg	2720	1.48	299 530.19	1.03	0.70
20	Accupril® 10mg	2422	1.32	374 127.89	1.29	0.98

CPI (Cost Prevalence Index) refer to chapter 4, section 4.8.2.4.

*These percentages were calculated as percentage of the total prevalence of all ACE inhibitor items and not the total prevalence of the top 20 ACE inhibitor items.

@ These percentages were calculated as percentage of the total cost of all ACE inhibitor items and not the total cost of the top 20 ACE inhibitor items.

As shown in table 5.4 the top item prescribed according to prevalence was the combination item Coversyl Plus® with 25 926 products. This product was followed by the Coversyl® generic namely Prexum®. The product with the highest total cost was Coversyl Plus® and contributed 21.94% (n=R5 467 572.61) of the total cost (N=R24 916 496.33) of the top 20 ACE inhibitors. The product with the lowest total cost was Pharmapress® 10mg with R265 711.35 as well as the lowest CPI of 0.30 which indicates that this product was the most inexpensive of all the top 20 products (refer to chapter 4, section 4.8.2.4). The product with the highest CPI was the combination item Zestoretic® 10/12.5mg with 2.88, which indicates that this product was the most expensive of all the products in the top 20 list. In addition to this there were 50% (n=10) of the top 20 items that had a CPI >1.

- *Year 2005*

Table 5.5: Prevalence and cost of the top 20 ACE inhibitor items according to prevalence for 2005

Position	Tradename	Frequency (N)	Frequency %*	Total cost (R)	Total cost %@	CPI#
1	Coversyl Plus®	21724	20.58	4 587 526.46	28.86	1.40
2	Prexum® 4mg	20577	19.49	2 963 546.15	18.65	0.96
3	Coversyl® 4mg	5778	5.47	810 301.65	5.10	0.93
4	Pharmapress Co®	4030	3.82	318 070.26	2.00	0.52
5	Accuretic® 20/12.5mg	3187	3.02	685 751.49	4.31	1.43
6	Pharmapress® 10mg	2908	2.75	124 030.18	0.78	0.28
7	Pharmapress® 20mg	2744	2.60	198 727.82	1.25	0.48
8	Tarka®	2487	2.36	708 434.98	4.46	1.89
9	Zetomax® 20mg	2135	2.02	170 933.87	1.08	0.53
10	Preterax®	2111	2.00	426 210.80	2.68	1.34
11	Tri-Plen Forte®	2090	1.98	588 750.92	3.70	1.87
12	Zetomax® 10mg	1959	1.86	99 031.76	0.62	0.34
13	Accuretic® 10/12.5mg	1860	1.76	267 434.04	1.68	0.96
14	Tritace® 5mg	1845	1.74	426 031.68	2.52	1.53
15	Tritace® 10mg	1779	1.69	462 655.74	2.91	1.73
16	Zestoretic® 20/12.5mg	1648	1.56	313 327.65	1.97	1.26
17	Co-Renitec®	1571	1.49	149 782.14	0.94	0.63
18	Tritace® 2.5mg	1550	1.47	264 788.70	1.67	1.13
19	Renitec® 10mg	1112	0.11	59 702.28	0.38	0.36
20	Tri-Plen®	1038	0.98	195 130.55	1.23	1.25

CPI (Cost Prevalence Index) refer to chapter 4, section 4.8.2.4.

*These percentages were calculated as percentage of the total prevalence of all ACE inhibitor items and not the total prevalence of the top 20 ACE inhibitor items.

@ These percentages were calculated as percentage of the total cost of all ACE inhibitor items and not the total cost of the top 20 ACE inhibitor items.

During 2005 the number one product prescribed according to prevalence was again Coversyl Plus® with 4202 less items prescribed (refer to table 5.5). This product also had the highest total cost and contributed 33.19% (n=R4 587 526.46) to the total cost (N=R13 820 169.12) of the top 20 ACE inhibitor items. Furthermore it can be seen that positions of the top 5 prescribed products during this period stayed exactly the same as the previous study period. Products with the lowest total cost (n=R59 702.28) came from new products on the top 20 list, namely Renitec® 10mg in position 19. Other new products on the list were Preterax® (position 10) and Tri-Plen® (position 20). Products no longer under the top 20 included Zestoretic® 10/12.5mg, Renitec® 20mg and Accupril® 10mg

The product with the highest CPI for this period was Tarka® with 1.89, which indicates that this product was the most expensive and the lowest CPI of 0.28 was again by Pharmapress® 10mg and indicated relatively inexpensive therapy. The number of products in the top 20 with a CPI

>1 was 50% (n=10), which is slightly lower than the previous period. Prexum® showed a higher CPI than that of Coversyl® which might have been the result where the average cost of the generic product was higher than that of the innovator product (refer to Appendix B, table B8 for the average costs).

- *Year 2006*

Table 5.6: Prevalence and cost of the top 20 items ACE inhibitor items according to prevalence for 2006

Position	Tradename	Frequency (N)	Frequency %*	Total cost (R)	Total cost %@	CPI#
1	Prexum® 4mg	14327	25.63	2 231 373.27	23.36	0.91
2	Prexum Plus®	9186	16.43	1 681 971.99	17.61	1.07
3	Coversyl Plus®	9161	16.39	2 006 796.07	21.01	1.28
4	Coversyl® 4mg	3014	5.39	454 859.78	4.76	0.88
5	Preterax®	1804	3.23	386 846.58	4.10	1.26
6	Tarka®	1505	2.69	461 857.76	4.83	1.80
7	Tri-Plen Forte®	1030	1.84	330 373.00	3.46	1.88
8	Pharmapress Co®	873	1.56	81 788.14	0.86	0.55
9	Accuretic® 20/12.5mg	777	1.39	174 670.58	1.83	1.32
10	Ramiwin® 5mg	697	1.25	122 111.27	1.28	1.03
11	Pharmapress® 10mg	686	1.23	32 922.53	0.34	0.28
12	Pharmapress® 20mg	670	1.19	55 035.02	0.58	0.46
13	Accuretic® 10/12.5mg	608	1.09	90 747.67	0.95	0.87
14	Ramiwin® 2.5mg caps.	548	0.98	53 920.22	0.56	0.58
15	Tri-Plen®	518	0.93	108 966.02	1.14	1.23
16	Enap-Co®	477	0.85	42 452.31	0.44	0.52
17	Tritace® 5mg	405	0.72	91 188.36	0.95	1.32
18	Co-Renitec®	384	0.69	43 325.26	0.45	0.66
19	Listoretic® 10/12.5mg	378	0.68	25 284.22	0.26	0.39
20	Perdix® 15mg	361	0.65	71 979.46	0.75	1.17

CPI (Cost Prevalence Index) refer to chapter 4, section 4.8.2.4.

*These percentages were calculated as percentage of the total prevalence of all ACE inhibitor items and not the total prevalence of the top 20 ACE inhibitor items.

@ These percentages were calculated as percentage of the total cost of all ACE inhibitor items and not the total cost of the top 20 ACE inhibitor items.

According to table 5.6 the item with the highest prevalence was the generic substitution of Coversyl®, namely Prexum® and this item had the highest total cost (n=R2 231 373.27) of all the top 20 items, and contributed 26.10% to the total cost (N=8 548 469.51) of the top 20 items. The item with the highest CPI was Tri-Plen Forte® with 1.88 which indicates that this item was relatively expensive (refer to chapter 4, section 4.9.2.4). The item with the lowest CPI of 0.28 was Pharmapress® 10mg, which indicates that this item was the most inexpensive of all the top 20 items.

The item with the lowest total cost (N=R25 284.22) was Listoretic® 10/12.5mg and two new items on the list included Ramiwin® 5mg (position 10) and Perdix® 15mg (position 20). The year 2006 also showed Prexum® to have a higher CPI than that of Coversyl® which might have been the result where the average cost of the generic product higher than that of the innovator product (refer to Appendix B, table B8 for the average costs). ACE inhibitors no longer under the top 20 in 2006 included Renitec® 10mg, Zestoretic® 20/12.5mg, Zetomax® 20mg, Zetomax® 10mg, Tritace® 10mg and Tritace® 2.5mg.

In addition to this 50% (n=10) of the top 20 items had a CPI >1.

It can be concluded from section 5.5 that the item with the highest CPI of all the items was Zestoretic® during 2004 and the item with the lowest CPI was Pharmapress® 10mg during 2005 and 2006. This section further revealed that although the CPI's of generic equivalents should be lower, there were products where the generic equivalents had higher CPI's, where the average cost per item of the generics were higher than that of the innovator equivalents.

Table 5.7: Prevalence of the top 5 ACE inhibitors on a yearly basis from 2001-2006

Position	2001-2002	2004	2005	2006
1	Coversyl®	Coversyl Plus®	Coversyl Plus®	Prexum®
2	Coversyl Plus®	Prexum®	Prexum®	Prexum Plus®
3	Zestoretic® 20/12.5mg	Coversyl®	Coversyl®	Coversyl Plus®
4	Accuretic® 20/12.5mg	Pharmapress Co®	Pharmapress Co®	Coversyl®
5	Tritace® 5mg	Accuretic® 20/12.5mg	Accuretic® 20/12.5mg	Preterax®

Table 5.7 reveal that Coversyl® as well as Coversyl Plus® were listed under the top 5 medicine items from 2001 until 2006. Prexum® however was listed three times under the top 5 medicine items. Prexum Plus® was only introduced into the market in 2006 and already it made it to the top 5 medicine items that same year. The fact that above mentioned tradenames all contain either perindopril of indapamide/perindopril showed the wide used of these products. This is further illustrated by the fact that twelve out of the top 20 ACE inhibitor products in table 5.7 contain perindopril (also refer to figure 5.4 for an illustration of the increasing high prevalence of these active ingredients). Accuretic® 20/12.5mg only came in three times under the top 5 medicine items, Pharmapress Co® two times, Tritace® 5mg, Zestoretic® 20/12.5mg and Preterax® only made it once into the top 5 medicine items.

5.6 Usage patterns and costs of the individual ACE inhibitor items

5.6.1 Introduction

In this section the prevalence and cost of the ACE inhibitors will be discussed according to active ingredient and the contribution made by total cost and prevalence of the single and combination items as well as the contribution made by the total cost and prevalence of the innovator and generic items to the total cost and prevalence of all the products containing the respective active ingredients. These contributions are summarised in table 5.8 to 5.18. The prevalence and cost of the individual ACE inhibitor products are listed in appendix B.

Table 5.8: Prevalence and cost of innovator and generic Benazepril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	58.02% (n=387)	41.98% (n=R70 786.14)	0	0	41.97% (n=280)	51.53% (n=R75 256.95)	0	0
2004	63.78% (n=368)	51.07% (n=R61 965.70)	0	0	36.22% (n=209)	48.93% (n=R59 359.27)	0	0
2005	39.04% (n=114)	27.03% (n=R17 978.88)	0	0	60.96% (n=178)	72.97% (n=R48 534.86)	0	0
2006	21.95% (n=45)	13.90% (n=R7 393.06)	0	0	78.05% (n=160)	86.10% (n=R45 787.37)	0	0
Jan-Apr 2004	68.35% (n=108)	58.21% (n=R19 917.70)	0	0	31.65% (n=50)	41.79% (n=R14 300.02)	0	0
May-Aug 2004	59.52% (n=125)	46.29% (n=R21 644.86)	0	0	40.48% (n=85)	53.71% (n=R25 114.82)	0	0
Sept-Dec 2004	64.59% (n=135)	50.57% (n=R20 403.14)	0	0	35.41% (n=74)	49.43% (n=R19 944.43)	0	0
Jan-Apr 2005	41.05% (n=39)	29.29% (n=R6 295.06)	0	0	58.95% (n=56)	70.71% (n=R15 198.23)	0	0
May-Aug 2005	38.14% (n=37)	26.33% (n=R5 809.58)	0	0	61.85% (n=60)	73.67% (n=R16 251.02)	0	0
Sept-Dec 2005	38.00% (n=38)	25.58% (n=R5 874.24)	0	0	62.00% (n=62)	74.42% (n=R17 085.61)	0	0
Jan-Apr 2006	23.94% (n=17)	15.46% (n=R2 871.68)	0	0	76.06% (n=54)	84.54% (n=R15 697.86)	0	0
May-Aug 2006	20.00% (n=14)	12.08% (n=R2 196.62)	0	0	80.00% (n=56)	87.92% (n=R15 985.30)	0	0
Sept-Dec 2006	21.88% (n=14)	14.15% (n=R2 324.76)	0	0	78.13% (n=50)	85.85% (n=R14 104.21)	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all benazepril containing medicine items

BENAZEPRIL

All the agents containing benazepril are either single agents or combination agents, and all the agents were innovators (also refer to table 5.8). For prevalence and cost of the individual benazepril ACE inhibitor products, refer to Appendix B, table B1.

According to table 5.8 the prevalence percentage of benazperil single item innovator items for year 2001 until 2006 shows a continuous decrease of 24.38% (n=254) from 2004 until 2005 and a further decrease of 17.09% (n=69) from 2005 until 2006. The total cost percentage also showed a continuous decrease of 24.04% (n= R43 986.82) from 2004 until 2005 and a decrease of 13.13% (n=R10 585.82) from 2005 until 2006.

Furthermore, table 5.8 showed that benazepril combination innovator items showed an increase of 24.74% although the number of items decreased by 31 from 2004 until 2005. The prevalence further increased by 17.09% and the number of items decreased by 18 from 2005 until 2006. The total cost contribution however showed an increase of 24.04% from 2004 until 2005 although the total cost decreased by R10 824.41 and the cost percentage increased by 17.09% from 2005 until 2006 where the total cost decreased by R2 747.49. The fact that the benazepril combination items showed constant increases in prevalence might be explained by the advantages of using combination therapy (refer to chapter 2, section 2.3.3).

Table 5.9: Prevalence and cost of innovator and generic Captopril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	13.89% (n=1882)	26.95% (n=R470 075.02)	66.73% (n=9043)	47.59% (n=R830 158.94)	3.52% (n=477)	67.58% (n=R117 891.73)	15.86% (n=2150)	18.71% (n=R326 428.95)
2004	4.56% (n=416)	9.32% (n=R62 465.97)	71.07% (n=6487)	53.72% (n=R359 911.62)	3.12% (n=285)	10.99% (n=R73 653.14)	21.25% (n=1940)	25.97% (n=R174 003.74)
2005	3.54% (n=127)	6.86% (n=R15 525.46)	57.59% (n=2064)	27.92% (n=R63 165.53)	7.90% (n=283)	30.18% (n=R68 275.40)	30.97% (n=1110)	35.03% (n=R79 257.29)
2006	2.39% (n=24)	3.72% (n=R3 662.84)	37.19% (n=373)	11.68% (n=R11 490.10)	17.65% (n=177)	49.14% (n=R48 347.69)	42.77% (n=429)	35.46% (n=R34 894.95)
Jan-Apr 2004	5.40% (n=136)	8.36% (n=R21 805.72)	72.88% (n=1835)	60.78% (n=R158 477.51)	3.85% (n=97)	9.84% (n=R25 659.84)	17.87% (n=450)	21.02% (n=R54 801.97)
May-Aug 2004	4.82% (n=145)	10.18% (n=R24 346.73)	68.97% (n=2076)	48.43% (n=R115 808.73)	4.68% (n=141)	15.49% (n=R37 032.41)	21.53% (n=648)	25.90% (n=R61 936.68)
Sept-Dec 2004	3.75% (n=135)	9.59% (n=R16 313.52)	71.55% (n=2576)	50.32% (n=R85 625.38)	1.31% (n=47)	6.44% (n=R10 960.89)	23.39% (n=842)	33.65% (n=R57 265.09)
Jan-Apr 2005	4.50% (n=55)	8.88% (n=R6 392.82)	57.00% (n=696)	30.67% (n=R22 080.71)	5.65% (n=69)	21.21% (n=R15 266.54)	32.84% (n=401)	39.24% (n=R28 253.59)
May-Aug 2005	3.80% (n=50)	7.79% (n=R6 538.06)	57.33% (n=755)	26.96% (n=R22 625.83)	8.28% (n=109)	31.16% (n=R26 150.35)	30.60% (n=403)	34.09% (n=R28 609.08)
Sept-Dec 2005	2.10% (n=22)	3.69% (n=R2 594.58)	58.60% (n=613)	26.25% (n=R18 458.99)	10.04% (n=105)	38.20% (n=R26 858.51)	29.25% (n=306)	31.85% (n=R22 394.62)
Jan-Apr 2006	3.06% (n=11)	3.43% (n=R1 108.34)	36.77% (n=132)	12.71% (n=R4 105.97)	16.71% (n=60)	44.38% (n=R14 332.82)	43.45% (n=156)	39.47% (n=R12 745.77)
May-Aug 2006	2.98% (n=10)	5.46% (n=R1 909.15)	34.82% (n=117)	10.97% (n=R3 837.31)	20.54% (n=69)	51.92% (n=R18 162.32)	41.67% (n=140)	31.66% (n=R11 074.43)
Sept-Dec 2006	0.97% (n=3)	2.07% (n=R645.35)	40.26% (n=124)	11.40% (n=R3 546.82)	15.58% (n=48)	50.94% (n=R15 852.55)	43.18% (n=133)	35.59% (n=R11 074.75)

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all captopril containing medicine items

CAPTOPRIL

All items containing captopril are either innovators or generics and single items or combination items (also refer to table 5.9). For prevalence and cost of the individual captopril containing ACE inhibitor products, refer to Appendix B, table B2.

According to table 5.9 the prevalence percentage of captopril containing single item innovators decreased by 1.02% (n=289) from 2004 until 2005 and then decreased further by 1.15% (n=103) from 2005 until 2006. The prevalence percentage of captopril containing single item generics showed a decrease of 13.48% (n=4423) from 2004 until 2005 and then decreased further by 20.40% (n=1691) from 2005 until 2006.

It can be concluded that the prevalence of the captopril containing generic items was consistently higher than the innovators, this might be due to mandatory generic substitution implemented in 2003 (refer to chapter 2, section 2.4.5).

Furthermore, the prevalence percentage of captopril containing combination innovator items increased by 4.78% although the number of items decreased by 2 from 2004 until 2005 and increased by 9.75% although the number of items decreased by 106 from 2005 until 2006. The captopril containing combination generic items also showed an increase of 9.72% while the number of items decreased by 830 and then increased further by 11.80% while the number of items decreased by 681 from 2005 until 2006.

Table 5.9 also showed that the total cost percentage of captopril containing single item innovators decreased by 2.46% (n=R46 940.51) from 2004 until 2005 and decreased further by 3.14% from 2005 until 2006. The cost percentage of captopril containing single item generics decreased by 25.80% (n=R296 746.09) from 2004 until 2005 and then decreased further by 16.24% (n=R51 675.43) from 2005 until 2006.

In addition to this the combination generic items increased by 9.06% although the total cost decreased by R94 746.45 from 2004 until 2005 and then increased even further by 0.43% whiles the total cost decreased by R44 362.34 from 2005 until 2006.

Table 5.10: Prevalence and cost of innovator and generic Cilazapril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence	Cost	Prevalence	Cost	Prevalence	Cost	Prevalence	Cost
2001-2002	56.42% (n=1586)	49.86% (n=R281 495.48)	0	0	43.58% (n=1225)	50.14% (n=R283 101.44)	0	0
2004	57.25% (n=1236)	53.72% (n=R212 297.58)	0	0	42.75% (n=923)	46.28% (n=R182 923.15)	0	0
2005	51.36% (n=303)	51.29% (n=R90 075.49)	0	0	48.64% (n=287)	48.71% (n=R43 879.46)	0	0
2006	47.83% (n=44)	53.73% (n=R8 613.99)	0	0	52.17% (n=48)	46.27% (n=R7 416.67)	0	0
Jan-Apr 2004	58.59% (n=406)	52.61% (n=R83 350.84)	0	0	41.41% (n=287)	47.39% (n=R75 083.56)	0	0
May-Aug 2004	59.23% (n=401)	56.02% (n=R68 179.67)	0	0	40.77% (n=276)	43.98% (n=R53 531.63)	0	0
Sept-Dec 2004	54.37% (n=429)	52.81% (n=R60 767.07)	0	0	45.63% (n=360)	47.19% (n=R54 307.96)	0	0
Jan-Apr 2005	53.00% (n=106)	52.03% (n=R15 649.05)	0	0	47.00% (n=94)	47.97% (n=R14 425.98)	0	0
May-Aug 2005	52.97% (n=107)	53.12% (n=R16 493.31)	0	0	47.03% (n=95)	46.88% (n=R14 554.58)	0	0
Sept-Dec 2005	47.87% (n=90)	48.54% (n=R14 053.67)	0	0	52.13% (n=98)	51.46% (n=R14 898.90)	0	0
Jan-Apr 2006	51.52% (n=17)	56.30% (n=R3 054.51)	0	0	48.48% (n=16)	43.70% (n=R2 370.43)	0	0
May-Aug 2006	53.13% (n=17)	57.62% (n=R3 193.48)	0	0	46.88% (n=15)	42.38% (n=R2 348.83)	0	0
Sept-Dec 2006	37.04% (n=10)	46.73% (n=R2 366.00)	0	0	62.96% (n=17)	53.27% (n=R2 697.41)	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all cilazapril containing medicine items

CILAZAPRIL

All agents containing cilazapril are either classified as single or combination items and all of the items are innovator items (also refer to table 5.10). For prevalence and cost of the individual cilazapril containing ACE inhibitor products, refer to Appendix B, table B3.

According to table 5.10 the prevalence percentage of cilazapril containing single item innovators showed a continuous decrease of 5.89% (n=933) from 2004 until 2005 and the prevalence percentage decreased further with 3.53% (n=259) from 2005 until 2006. The prevalence percentage of the combination innovator items increased by 5.89% although the number of items decreased by 636 from 2004 until 2005 and a further increase of 3.53% and the number of items decreased further by 239 from 2005 until 2006. The increase in percentage and the reduction in the number of combination innovator items might be attributed to the reduction in the total prevalence of all cilazapril containing items from 1569 from 2004 until 2005 and 498 from 2005 until 2006 (see table 5.10). In addition to this the prevalence contribution of the combination innovator items was higher than the single items during 2006. The results revealed an increased use in combination items from 2004 until 2006.

The total cost contribution of cilazapril containing single items innovators decreased by 2.43% (n=R122 222.09) from 2004 until 2005 and then increased by 2.44% although the total cost decreased by R81 461.50 from 2005 until 2006. The cost percentage by cilazapril containing combination innovators increased by 2.43% from 2004 until 2005 and 2.44% from 2005 until 2006, but the total cost of these items showed a continuous decrease of R139 043.69 from 2004 until 2005 and R36 462.79 from 2005 until 2006. This might be attributed to the continuous decrease in the number of cilazapril containing combination items from 2004 until 2006.

Table 5.11: Prevalence and cost of innovator and generic Enalapril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	30.53% (n=13015)	30.26% (n=R2 176 140.34)	40.42% (n=17233)	32.29% (n=R2 321 808.41)	19.45% (n=8295)	27.33% (n=R1 964 838.06)	9.60% (n=4094)	10.12% (n=R727 586.95)
2004	18.56% (n=7230)	17.40% (n=R544 242.90)	49.09% (n=19127)	40.18% (n=R1 256 969.07)	12.21% (n=4757)	18.03% (n=R564 051.15)	20.14% (n=7846)	24.39% (n=R762 827.85)
2005	14.56% (n=2827)	13.51% (n=R169 141.89)	51.42% (n=9981)	42.78% (n=R535 779.72)	8.09% (n=1571)	11.96% (n=R149 782.14)	25.92% (n=5031)	31.75% (n=R397 576.80)
2006	8.42% (n=677)	12.74% (n=R48 389.66)	35.00% (n=2815)	43.15% (n=R163 914.05)	4.78% (n=384)	11.41% (n=R43 325.26)	16.79% (n=1350)	32.71% (n=R124 240.45)
Jan-Apr 2004	21.14% (n=2305)	17.57% (n=R201 848.84)	48.46% (n=5284)	40.96% (n=R470 467.14)	13.33% (n=1454)	17.67% (n=R202 911.64)	17.07% (n=1861)	23.80% (n=R273 422.77)
May-Aug 2004	19.59% (n=2442)	19.42% (n=R189 450.10)	47.49% (n=5921)	38.04% (n=R371 093.13)	13.12% (n=1634)	19.99% (n=R195 024.06)	19.81% (n=2470)	22.55% (n=R219 994.67)
Sept-Dec 2004	15.92% (n=2483)	15.24% (n=R152 943.96)	50.82% (n=7922)	41.38% (n=R415 408.80)	10.71% (n=1669)	16.55% (n=R166 115.45)	22.55% (n=3515)	26.84% (n=R269 410.41)
Jan-Apr 2005	16.60% (n=1005)	15.70% (n=R60 869.16)	49.72% (n=3010)	40.67% (n=R157 669.15)	9.70% (n=587)	14.65% (n=R56 810.23)	23.98% (n=1452)	28.98% (n=R112 330.78)
May-Aug 2005	14.36% (n=1007)	13.25% (n=R59 849.08)	51.52% (n=3612)	42.93% (n=R193 917.02)	7.79% (n=546)	11.41% (n=R51 560.66)	26.33% (n=1846)	32.41% (n=R146 384.24)
Sept-Dec 2005	12.84% (n=815)	11.73% (n=R48 423.65)	52.94% (n=3359)	44.61% (n=R184 193.55)	6.90% (n=438)	10.03% (n=R41 411.25)	27.31% (n=1733)	33.63% (n=R138 861.78)
Jan-Apr 2006	13.01% (n=234)	12.83% (n=R16 506.09)	55.25% (n=994)	45.37% (n=R58 358.70)	7.00% (n=126)	11.27% (n=R14 491.11)	24.74% (n=445)	30.53% (n=R39 263.01)
May-Aug 2006	13.02% (n=229)	12.64% (n=R16 074.30)	53.55% (n=942)	43.25% (n=R55 001.48)	7.79% (n=137)	11.78% (n=R14 977.71)	25.64% (n=451)	32.33% (n=R41 116.49)
Sept-Dec 2006	12.83% (n=214)	12.74% (n=R15 809.27)	52.70% (n=879)	40.72% (n=R50 553.87)	7.25% (n=121)	11.17% (n=R13 856.44)	27.22% (n=454)	35.35% (n=R43 860.95)

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all enalapril containing medicine items

ENALAPRIL

All agents containing enalapril are either classified as single or combination items and all of the items are either innovator or generic items (also refer to table 5.11).

For prevalence and cost of the individual enalapril containing ACE inhibitor products, refer to Appendix B table B4.

As shown in table 5.11 the prevalence of enalapril containing single items innovators decreased by 4.00% (n=4403) from 2004 until 2005 and then decreased further by 6.14% (n=2150) from 2005 until 2006. The prevalence percentage of enalapril containing single item generics increased by 2.33% although the number of items decreased by 9146 from 2004 until 2005 and then decreased by 16.42% (n=7166) from 2005 until 2006.

It can be concluded that the prevalence of enalapril containing generic items was consistently higher than that of the innovator items.

In addition to this the combination innovators showed a decrease of 4.12% (n=3186) from 2004 until 2005 and then decreased by 3.37% (n=1187) from 2005 until 2006. The prevalence percentage of enalapril containing combination generic items showed an increase of 5.78% although the number of items decreased by 2815 from 2004 until 2005 and then decreased by 9.13% (n=3681) from 2005 until 2006.

Furthermore, the total cost contribution of enalapril containing single item innovators showed a decrease of 3.89% (n=R375 101.01) from 2004 until 2005 and then decreased again by 0.77% (n=R120 752.23) from 2005 until 2006. The cost percentage of generic single items however increased by 2.60% although the total cost decreased by R721 189.35 from 2004 until 2005 and then increased further by 0.37% although the total cost decreased by R371 865.67 from 2005 until 2006.

Table 5.11 further reveal that enalapril containing combination innovators showed a decrease in total cost percentage of 6.07% (n=R414 269.01) from 2004 until 2005 and then decreased again by 0.55% (n=R106 456.88) from 2005 until 2006. Enalapril containing combination generic items showed an increase in cost contribution of 31.75% (n=R365 251.05) from 2004 until 2005 and then increased further by 0.96% (n=R273 336.35) from 2005 until 2006.

It can be concluded that the prevalence of enalapril containing combination generics was also consistently higher than the innovators from 2004 until 2006. This showed an increase in the use of items containing enalapril and might be due to the health care professional realising the advantages of using generic items such as possible cost savings for the patient (also refer to chapter 2, section 2.4) as well as the law making it mandatory for the pharmacist to inform the patient about generic substitution (also refer to chapter 2, section 2.4.5).

Table 5.12: Prevalence and cost of innovator and generic Fosinopril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	69.60% (n=2347)	65.60% (n=R468 708.02)	0	0	30.40% (n=1025)	34.40% (n=R245 742.40)	0	0
2004	61.45% (n=1387)	57.47% (n=R280 390.29)	0	0	38.55% (n=870)	42.53% (n=R207 481.83)	0	0
2005	69.48% (n=478)	64.83% (n=R89 338.48)	0	0	30.52% (n=210)	35.12% (n=R48 463.01)	0	0
2006	53.78% (n=64)	50.26% (n=R11 073.21)	21.01% (n=25)	15.95% (n=R3 513.88)	25.21% (n=30)	33.79% (n=R7 443.71)	0	0
Jan-Apr 2004	63.28% (n=455)	59.96% (n=R102 613.17)	0	0	36.72% (n=264)	40.04% (n=R68 514.41)	0	0
May-Aug 2004	60.67% (n=455)	56.14% (n=R93 168.62)	0	0	39.33% (n=295)	43.86% (n=R72 791.00)	0	0
Sept-Dec 2004	60.53% (n=477)	56.11% (n=R84 608.50)	0	0	39.47% (n=311)	43.89% (n=R66 176.42)	0	0
Jan-Apr 2005	66.95% (n=160)	62.94% (n=R29 968.29)	0	0	33.05% (n=79)	37.06% (n=R17 643.97)	0	0
May-Aug 2005	70.97% (n=176)	65.72% (n=R33 028.24)	0	0	29.03% (n=72)	34.28% (n=R17 226.17)	0	0
Sept-Dec 2005	68.60% (n=142)	65.96% (n=R26341.95)	0	0	29.35% (n=59)	34.03% (n=R13592.87)	0	0
Jan-Apr 2006	76.74% (n=33)	72.45% (n=R6 422.63)	0	0	30.30% (n=10)	27.55% (n=R2 442.34)	0	0
May-Aug 2006	52.27% (n=23)	45.74% (n=R3 398.44)	22.72% (n=10)	19.13% (n=R1 421.26)	25.00% (n=11)	35.13% (n=R2 610.11)	0	0
Sept-Dec 2006	25.00% (n=8)	21.83% (n=R1 252.14)	46.88% (n=15)	36.48% (n=R2 092.62)	28.13% (n=9)	41.69% (n=R2 391.62)	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all fosinopril containing medicine items

FOSINOPRIL

All the fosinopril agents in this group are innovators, but they can either be single agents or combination agents (also refer to table 5.12), except for 2006 when generic innovator items were introduced into the market. For prevalence and cost of the individual fosinopril ACE inhibitor products, refer to Appendix B table B5.

As shown in table 5.12 the prevalence percentage of fosinopril containing single item innovators increased by 8.03% although the number of items decreased by 909 from 2004 until 2005. The fact that the number of items decreased while the percentage increased might be attributed to the total prevalence of all fosinopril containing items decreasing from 2257 items in 2004 to 688 in 2005 (see table 5.12). The prevalence percentage then decreased by 15.70% (n=414) from 2005 until 2006. Furthermore, the prevalence percentage of fosinopril containing combination innovator items showed a continuous decrease of 8.03% (n=660) from 2004 until 2005 and 5.31% (n=180) from 2005 until 2006. The decrease in prevalence from 2005 until 2006 might be attributed to the introduction of fosinopril containing single item generics.

According to table 5.12 the total cost percentage of fosinopril containing single innovator items increased by 7.36% although the total cost decreased by R191 051.81 from 2004 until 2005 and then decreased by 14.57% (n=R78 265.27) from 2005 until 2006. The fosinopril containing combination generic items showed a reduction in cost percentage of 7.41% (n=R159 018.82) from 2004 until 2005 and a further reduction of 1.33% (n=R41 019.30) from 2005 until 2006. The period of May 2006 until August 2006 showed the introduction of the generic items and these items showed an increase of 24.16% (n=5) in prevalence contribution and the total cost contribution also increased by 17.35% (n=R671.36) from May-August 2006 to September-December 2006. In addition to this the prevalence and cost contribution was higher than that of fosinopril containing innovator items in September-December 2006.

Table 5.13: Prevalence and cost of innovator and generic Lisinopril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	16.14% (n=5659)	16.10% (n=R 1044 655.93)	42.87% (n=15031)	30.00% (n=R1 946 948.82)	40.99% (n=14371)	53.90% (n=R3 497 881.31)	0	0
2004	9.53% (n=2225)	7.30% (n=R229 166.79)	63.14% (n=14746)	35.00% (n=R1 098 349.19)	35.89% (n=8382)	57.69% (n=R1 810 423.66)	0	0
2005	7.54% (n=734)	6.42% (n=R57 111.25)	60.18% (n=5860)	39.92% (n=R355 156.39)	27.20% (n=2649)	48.28% (n=R429 491.76)	5.08% (n=495)	5.38% (n=R47 894.12)
2006	4.45% (n=112)	3.84% (n=R8 518.59)	34.63% (n=871)	27.53% (n=R61 119.07)	16.62% (n=418)	20.72% (n=R45 996.00)	44.29% (n=1114)	47.91% (n=R106 350.22)
Jan-Apr 2004	10.36% (n=825)	9.52% (n=R116 559.47)	55.27% (n=4403)	32.14% (n=R393 511.87)	34.37% (n=2738)	58.34% (n=R714 416.10)	0	0
May-Aug 2004	8.51% (n=697)	7.78% (n=R79 628.81)	59.28% (n=4855)	37.07 (n=R379 412.44)	32.21% (n=2638)	55.15% (n=R564 457.72)	0	0
Sept-Dec 2004	7.64% (n=703)	6.54% (n=R59 978.51)	59.67% (n=5488)	35.49% (n=R325 424.88)	32.68% (n=3006)	57.97% (n=R531 549.84)	0	0
Jan-Apr 2005	9.14% (n=279)	7.29% (n=R22 409.87)	58.79% (n=1795)	34.68% (n=R107 508.11)	32.07% (n=979)	58.09% (n=R180 083.23)	0	0
May-Aug 2005	7.50% (n=259)	6.25% (n=R21 392.04)	61.31% (n=2117)	37.69% (n=R128 950.63)	28.32% (n=978)	52.68% (n=R180 235.86)	2.87% (n=99)	3.38% (n=R11 574.15)
Sept-Dec 2005	6.06% (n=196)	5.60% (n=R13 309.34)	60.27% (n=1948)	49.98% (n=R118 697.65)	21.41% (n=692)	29.13% (n=R69 172.67)	12.25% (n=396)	15.29% (n=R36 319.67)
Jan-Apr 2006	5.50% (n=42)	13.69% (n=R1 0096.53)	37.17% (n=284)	27.29% (n=R20 127.66)	19.24% (n=147)	21.45% (n=R15 818.28)	38.09% (n=291)	37.58% (n=R27 714.04)
May-Aug 2006	4.44% (n=38)	3.87% (n=R2 886.29)	34.46% (n=295)	27.54% (n=R20 551.94)	16.00% (n=137)	19.84% (n=R14 806.51)	45.09% (n=386)	48.76% (n=R36 390.26)
Sept-Dec 2006	3.58% (n=32)	2.94% (n=R2 362.43)	32.63% (n=292)	25.42% (n=R20 439.47)	14.97% (n=134)	19.11% (n=R15 371.21)	48.83% (n=437)	52.53% (n=R42 245.92)

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all lisinopril containing medicine items

LISINOPRIL

All items in this section are either single items or combination items and they are either innovators or generics (also refer to table 5.13). For prevalence and cost of the individual lisinopril containing ACE inhibitor products, refer to Appendix B table B6.

According to table 5.13 lisinopril containing single items showed a decrease in the prevalence percentage of 1.99% (n=1491) from 2004 until 2005 and then a further decrease of 3.09% (n=622) from 2005 until 2006. The lisinopril containing generic single items also showed a decrease in prevalence percentage of 2.96% (n=8886) from 2004 until 2005 and then decreased further by 25.55% (n=4989) from 2005 until 2006. Lisinopril containing combination innovator items showed a decrease of 8.69% (n=5733) from 2004 until 2005 and a further decrease of 10.58% (n=2231) from 2005 until 2006.

Furthermore, May 2005 until August 2005 showed the introduction of lisinopril containing combination generic items and these items showed an increase in prevalence of 39.21% (n=619) from 2005 until 2006.

Table 5.13 also reveals a decrease in the cost percentage of lisinopril containing single item innovators decreased by 0.88% (n=R172 055.54) from 2004 until 2005 and 2.58% (n=R48 592.66) from 2005 until 2006. Lisinopril containing generic single items showed a decrease of 4.92% although the total cost decreased by R743 192.80 from 2004 until 2005. From 2005 until 2006 it decreased further with 12.39% (n=R294 037.32). The total cost percentage of the lisinopril containing combination innovator items decreased by 9.41% (n=R1 380 931.90) from 2004 until 2005 and then decreased further by 27.56% (n=R383 495.76) from 2005 until 2006. The combination generic items showed an increase of 42.53% (n=R58 456.10) from 2005 until 2006.

It can be concluded that although the cost and prevalence of single items and lisinopril containing combination innovator items decreased, lisinopril containing generic combination items have shown an increase in prevalence and cost contribution since they were introduced during 2005.

Table 5.14: Prevalence and cost of innovator and generic Moexipril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	100.00% (n=9)	100.00% (n=R1 124.73)	0	0	0	0	0	0
2004	100.00% (n=791)	100.00% (n=R115 983.25)	0	0	0	0	0	0
2005	100.00% (n=874)	100.00% (n=R132 223.00)	0	0	0	0	0	0
2006	100.00% (n=701)	100.00% (n=R110 749.58)	0	0	0	0	0	0
Jan-Apr 2004	100.00% (n=104)	100.00% (n=R14 369.75)	0	0	0	0	0	0
May-Aug 2004	100.00% (n=342)	100.00% (n=R52 206.27)	0	0	0	0	0	0
Sept-Dec 2004	100.00% (n=345)	100.00% (n=R49 407.23)	0	0	0	0	0	0
Jan-Apr 2005	100.00% (n=287)	100.00% (n=R43 241.25)	0	0	0	0	0	0
May-Aug 2005	100.00% (n=322)	100.00% (n=R48 958.42)	0	0	0	0	0	0
Sept-Dec 2005	100.00% (n=265)	100.00% (n =R40 023.33)	0	0	0	0	0	0
Jan-Apr 2006	100.00% (n=255)	100.00% (n=R40 137.42)	0	0	0	0	0	0
May-Aug 2006	100.00% (n=242)	100.00% (n=R37 726.20)	0	0	0	0	0	0
Sept-Dec 2006	100.00% (n=204)	100.00% (n=R32 885.96)	0	0	0	0	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all moexipril containing medicine items

MOEXIPRIL

All the moexipril agents are single agents and innovators for all the respective study periods (also refer to table 5.14). This means that all the items contributed 100% to the total cost and prevalence of moexipril containing items. For prevalence and cost of the individual moexipril containing ACE inhibitor products, refer to Appendix B table B7.

According to table 5.14 the prevalence of moexipril containing innovators increased by 83 items from 2004 until 2005 and then showed a decrease of 173 items from 2005 until 2006. Furthermore, the highest number of items claimed was during September until December 2004, which was during the "full" implementation of the single exit price (refer to chapter 3, section 3.4.2.3) and showed the lowest average cost per item (refer to Appendix B, table B7).

Table 5.14 further shows that total cost of all moexipril containing items increased by R162 39.75 from 2004 until 2005 and then decreased by R21 473.42 from 2005 until 2006.

Table 5.15: Prevalence and cost of innovator and generic Perindopril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	70.81% (n=30031)	68.55% (n=R6 528 300.76)	0	0	29.19% (n=12378)	31.45% (n=R2 995 329.77)	0	0
2004	20.94% (n=12793)	19.94% (n=R2 148 208.06)	34.31% (n=20959)	26.70% (n=R2 875 557.50)	44.75% (n=27337)	53.36% (n=R5 746 925.40)	0	0
2005	11.51% (n=5778)	33.71% (n=R810 301.65)	40.98% (n=20577)	33.71% (n=R2 963 546.15)	47.47% (n=23835)	57.02% (n=R5 013 737.26)	0.04% (n=21)	0.05% (n=R4 731.05)
2006	8.57% (n=3243)	7.58% (n=R519 357.51)	37.88% (n=14327)	32.58% (n=R2 231 373.27)	53.27% (n=20151)	59.50% (n=R4 075 614.64)	0.28% (n=106)	0.34% (n=R22 979.56)
Jan-Apr 2004	27.86% (n=3832)	25.88% (n=R698 167.31)	26.30% (n=3618)	20.44% (n=R551 480.92)	45.84% (n=6306)	53.68% (n=R1 448 198.86)	0	0
May-Aug 2004	24.13% (n=5049)	24.45% (n=R947 309.90)	31.20% (n=6528)	23.17% (n=R897 603.98)	44.66% (n=9344)	52.39% (n=R2 029 867.07)	0	0
Sept-Dec 2004	14.81% (n=3912)	11.98% (n=R502 730.85)	40.94% (n=10813)	33.98% (n=R1 426 472.60)	44.25% (n=11687)	54.05% (n=R2 268 859.47)	0	0
Jan-Apr 2005	13.06% (n=1956)	10.42% (n=R268 616.43)	39.63% (n=5934)	32.66% (n=R841 986.98)	47.30% (n=7082)	56.92% (n=R1 467 221.99)	0	0
May-Aug 2005	11.32% (n=2026)	9.10% (n=R283 382.45)	41.53% (n=7432)	33.96% (n=R1 057 110.49)	47.14% (n=8436)	56.93% (n=R1 772 172.87)	0	0
Sept-Dec 2005	10.30% (n=1796)	8.33% (n=R258 302.77)	41.88% (n=7301)	34.32 (n=R1 064 448.68)	47.70% (n=8317)	57.20% (n=R1 774 342.40)	0.12% (n=21)	0.15 (n=R4 731.05)
Jan-Apr 2006	8.99% (n=1048)	7.21% (n=R156 263.94)	40.34% (n=4701)	33.95% (n=R735 282.17)	50.28% (n=5860)	58.37% (n=R1 264 449.38)	0.39% (n=45)	0.47% (n=10 096.53)
May-Aug 2006	7.17% (n=1068)	7.17% (n=R163 151.23)	38.04% (n=4870)	33.24% (n=R756 719.35)	53.39% (n=6834)	59.32% (n=R1 350 413.09)	0.23% (n=29)	0.27% (n=R6 061.63)
Sept-Dec 2006	8.42% (n=1127)	8.31% (n=R199 942.34)	35.57% (n=4756)	30.72% (n=R739 371.75)	55.77% (n=7457)	60.69% (n=R1 460 752.17)	0.24% (n=32)	0.28% (n=R6 821.40)

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all moexipril containing medicine items

PERINDOPRIL

All the items in this section are either innovator or generic items and these items are either single items or combination items (refer to table 5.15). For prevalence and cost of the individual perindopril containing ACE inhibitor products, refer to Appendix B table B8.

According to table 5.15 perindopril containing single item innovator items showed a decrease in prevalence of 9.43% (n=7015) from 2004 until 2005 and a decrease of 2.94% (n=2535) from 2005 until 2006. The perindopril containing generic single items increased by 6.67% although the number of items decreased by 382 from 2004 until 2005 and then decreased by 3.10% (n=6250) from 2005 until 2006. The prevalence of the generic single items was consistently higher than that of the innovator items from 2004 until 2006.

Perindopril containing combination innovator items showed an increase of 2.72% although the number of items decreased by 3502 from 2004 until 2005 and then the percentage increased by 5.80% while the number of items further decreased by 3684 from 2005 until 2006. The perindopril containing combination generic items were introduced into the market in 2005 and these items showed an increase in prevalence contribution of 0.24% (n=85) from 2005 until 2006.

Table 5.15 also shows that the total cost percentage of perindopril containing single item innovators increased by 13.77% although the total cost of these items decreased by R1 337 906.41 from 2004 until 2005 and then decreased by 26.13% (n=R290 944.14) from 2005 until 2006. The perindopril containing generic single items showed an increase in contribution of 7.01% (n=R87 988.65) from 2004 until 2005 and a reduction of 1.13% (n=R732 172.88) from 2005 until 2006. In addition to this the total cost percentage of perindopril containing combination innovators consistently increased by 3.66% from 2004 until 2005 and 5.80% from 2005 until 2006 while the total cost consistently decreased by R733 188.14 from 2004 until 2005 and R938 133.62 from 2005 until 2006. Perindopril containing combination generic items also showed an increase in cost contribution of 0.29% (n=R18 248.51) from 2005 until 2006.

It can be concluded from this section that perindopril containing combination innovator items showed a consistently higher prevalence than the single items. This might be attributed to realisation of the advantages of using combination items (refer to chapter 2, section 2.3.3).

Table 5.16: Prevalence and cost of innovator and generic Quinapril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	36.12% (n=8954)	33.90% (n=R1 663 291.88)	0	0	63.88% (n=15839)	66.10% (n=R3 242 778.37)	0	0
2004	33.16% (n=5530)	30.65% (n=R1 011 415.86)	0	0	66.84% (n=11149)	69.35% (n=R2 287 950.94)	0	0
2005	27.69% (n=1933)	26.89% (n=R350 567.26)	0	0	72.31% (n=5047)	73.11% (n=R953 185.53)	0	0
2006	15.18% (n=328)	15.25% (n=R57 175.32)	3.15% (n=68)	2.32% (n=R8 713.48)	64.09% (n=1385)	70.77% (n=R265 418.25)	17.58% (n=380)	11.65% (n=R43 700.80)
Jan-Apr 2004	35.13% (n=1776)	32.65% (n=R382 916.31)	0	0	64.87% (n=3280)	67.35% (n=R789 738.40)	0	0
May-Aug 2004	33.16% (n=1747)	30.05% (n=R312 304.84)	0	0	66.84% (n=3521)	69.95% (n=R726 910.81)	0	0
Sept-Dec 2004	31.58% (n=2007)	29.08% (n=R316 194.71)	0	0	68.42% (n=4348)	70.92% (n=R771 301.73)	0	0
Jan-Apr 2005	27.60% (n=668)	27.60% (n=R118 284.92)	0	0	71.60% (n=1684)	72.40% (n=R310 233.26)	0	0
May-Aug 2005	27.59% (n=691)	27.27% (n=R128 746.39)	0	0	72.40% (n=1813)	72.73% (n=R343 406.45)	0	0
Sept-Dec 2005	27.02% (n=574)	25.69% (n=R103 535.95)	0	0	72.98% (n=1550)	74.31% (n=R299 545.82)	0	0
Jan-Apr 2006	17.97% (n=133)	19.54% (n=R31 738.76)	0.81% (n=6)	0.39% (n=R625.20)	81.22% (n=601)	80.08% (n=R130 092.72)	0	0
May-Aug 2006	14.34% (n=104)	11.75% (n=R14 449.52)	4.00% (n=29)	3.15% (n=R3 873.19)	76.00% (n=551)	81.23% (n=R99 934.32)	5.66% (n=41)	3.87% (n=R4 766.33)
Sept-Dec 2006	13.08% (n=91)	12.27% (n=R10 987.04)	4.74% (n=33)	4.71% (n=R4 215.09)	33.48% (n=233)	39.53% (n=R3 5391.21)	48.71% (n=339)	43.49% (n=R38 934.47)

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all quinapril containing medicine items

QUINAPRIL

All the items in this section are either innovator or generic items and these items are either single items or combination items (refer to table 5.16). For prevalence and cost of the individual quinapril containing ACE inhibitor products, refer to Appendix B table B9.

Table 5.16 shows a continuous decrease in the prevalence percentage of 5.49% (n=3597) from 2004 until 2005 and 12.51% (n=1605) from 2005 until 2006. Quinapril containing combination innovator items showed a continuous increase in contribution of 2.96% although the number of items decreased by 4690 from 2004 until 2005. The prevalence percentage increased further by 5.47% while the number of items decreased further by 6102 from 2005 until 2006. The prevalence of quinapril containing combination innovators items were consistently higher than that of quinapril containing single item innovators. During 2006 single items and combination item generics were introduced into the market.

In addition to table 5.16 the cost percentage of all quinapril containing single item innovators decreased by 3.76% (n=R660 848.60) from 2004 until 2005 and then decreased further by 11.64% (n=R293 391.94) from 2005 until 2006. The total cost percentage of quinapril containing combination item innovators showed an increase of 3.76% from 2004 until 2005 although the total cost decreased by R1 334 765.41 and the total cost contribution increased even further by 2.34% while the total cost decreased by R687 767.28 from 2005 until 2006.

Furthermore, with the introduction of quinapril containing single item generics in January-April 2006, the prevalence of these items increased by 3.19% (n=23) until May-August 2006 and then increased further by 0.74% (n=4) until September-December 2006. The generic combination items also showed an increase of 43.05% (n=298) from May-August until September-December 2006. The total cost contribution of quinapril containing single item generics increased by 2.76% (n=R3 247.99) from January-April 2006 and increased further by 1.56% (n=R341.90) from May-August 2006 until September-December 2006. The combination generic items increased by 39.62% (n=R34 168.14) from May-August 2006 until September-December 2006.

It can be concluded that quinapril containing generic items have shown a continuous increase in prevalence since they were introduced in 2006.

Table 5.17: Prevalence and cost of innovator and generic Ramipril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	81.78% (n=22688)	93.13% (n=R5 485 929.73)	0	0	18.22% (n=5055)	6.87% (n=R404 403.63)	0	0
2004	71.15% (n=15966)	69.06% (n=R3 932 995.22)	2.80% (n=628)	2.54% (n=R144 886.60)	0.00% (n=1)	0.00% (n=R198.13)	0	0
	0	0	0	0	26.05% (n=5845)	28.39% (n=R1616 923.05)	0	0
2005	54.95% (n=5571)	54.81% (n=R1 211 303.50)	14.19% (n=1439)	9.73% (n=R215 008.36)	30.85% (n=3128)	35.47% (n=R783 881.47)	0	0
2006	23.99% (n=1037)	23.66% (n=R219 292.44)	40.19% (n=1737)	28.93% (n=R268 109.72)	35.82% (n=1548)	47.41% (n=R439 339.02)	0	0
Jan-Apr 2004	72.77% (n=5244)	69.54% (n=R1 479 784.30)	1.05% (n=76)	1.10% (n=R23 341.64)	26.17% (n=1886)	29.36% (n=R624 745.15)	0	0
May-Aug 2004	71.10% (n=5186)	69.97% (n=R1 325 463.54)	2.85% (n=208)	2.64% (n=R49 981.56)	26.05% (n=1900)	27.39% (n=R518 885.19)	0	0
Sept-Dec 2004	69.72% (n=5536)	67.42% (n=R1 127 747.38)	4.33% (n=344)	4.28% (n=R71 563.40)	0.01% (n=1)	0.01% (n=R198.13)	0	0
	0	0	0	0	25.93% (n=2059)	28.29% (n=R473 292.71)	0	0
Jan-Apr 2005	64.08% (n=2110)	62.26% (n=R463 210.92)	5.89% (n=194)	5.10% (n=R37 974.12)	30.03% (n=989)	32.64% (n=R242 848.76)	0	0
May-Aug 2005	55.94% (n=2001)	55.39% (n=R436 352.37)	12.19% (n=436)	8.33% (n=R65 593.74)	31.87% (n=1140)	36.28% (n=R285 784.27)	0	0
Sept-Dec 2005	44.68% (n=1460)	45.95% (n=R311 740.21)	24.76% (n=809)	16.43 (n=R111 440.50)	30.57% (n=999)	37.62% (n=R255 248.44)	0	0
Jan-Apr 2006	28.97% (n=418)	27.88% (n=R92 115.17)	34.10% (n=492)	22.63% (n=R74 770.31)	36.94% (n=533)	49.49% (n=R163 521.42)	0	0
May-Aug 2006	22.15% (n=324)	21.36% (n=R65 878.85)	42.58% (n=623)	30.96% (n=R95 492.39)	35.27% (n=516)	47.68% (n=R147 088.05)	0	0

Table 5.17 (continued): Prevalence and cost of innovator and generic Ramipril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
Sept-Dec 2006	20.98% (n=295)	20.61% (n=R61 298.42)	44.24% (n=622)	32.90% (n=R97 847.02)	34.78% (n=489)	46.49% (n=R138 282.86)	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all ramipril containing medicine items

RAMIPRIL

All items in this section are either single item innovators or generics or they can be combination innovator items. This is however no ramipril containing combination item generic in this section (refer to table 5.17). For prevalence and cost of the individual ramipril containing ACE inhibitor products, refer to Appendix B table B10.

According to table 5.17 the prevalence percentage of ramipril containing single item innovators decreased by 16.20% (n=10395) from 2004 until 2005 and then decreased by 30.96% (n=4534) from 2005 until 2006. The ramipril containing generic single items however showed an increase of 11.39% (n=811) from 2004 until 2005 and an increase of 26.00% (n=300) from 2005 until 2006. In 2006 the prevalence of ramipril containing single item generics was higher than that of the innovators, which shows an increase in the use of the generic items. Furthermore, the prevalence percentage of ramipril containing combination innovator items increased by 4.80% from 2004 until 2005 while the number of items decreased by 2717 and the contribution further increased by 4.97% while the number of items decreased further by 1580 from 2005 until 2006.

Table 5.17 also showed that ramipril was the only active ingredient which had two different combination innovator items namely ramipril/HCTZ and felodipine/ramipril (also refer to Appendix B, table B10).

The cost percentage by the ramipril containing single item innovators decreased by 14.28% (n=R2 721 651.72) from 2004 until 2005 and decreased further by 31.15% (n=R992 011.06) from 2005 until 2006. The ramipril containing generic cost percentage was consistently lower than that of the innovator single items but showed an increase of 7.19% (n=R70 121.76) from 2004 until 2005 and then increased by 19.20% (n=R53 101.36) from 2005 until 2006. The combination innovator cost contribution showed an increase of 7.08% but the total cost decreased by R833 239.71 from 2004 until 2005 and a further increase of 11.94% although the total cost decreased by R344 542.45 from 2005 until 2006.

Table 5.18: Prevalence and cost of innovator and generic Trandolapril containing items from 2001-2006

Period	Single items				Combination items			
	Innovators		Generics		Innovators		Generics	
	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*	Prevalence*	Cost*
2001-2002	29.09% (n=1707)	27.34% (n=R499 834.03)	0	0	70.91% (n=4160)	72.66% (n=R1 328 582.63)	0	0
2004	20.87% (n=957)	13.61% (n=R170 381.48)	0	0	71.13% (n=3628)	86.39% (n=R1 081 418.51)	0	0
2005	18.88% (n=579)	10.65% (n=R84 421.58)	0	0	81.12% (n=2487)	89.35% (n=R708 434.98)	0	0
2006	13.46% (n=234)	7.46% (n=R37 253.64)	0	0	86.54% (n=1505)	92.54% (n=461 857.76)	0	0
Jan-Apr 2004	22.42% (n=287)	14.90% (n=R58 696.07)	0	0	77.58% (n=993)	85.10% (n=R335 363.97)	0	0
May-Aug 2004	19.26% (n=295)	12.79% (n=R55 937.55)	0	0	80.74% (n=1237)	87.21% (n=R381 587.09)	0	0
Sept-Dec 2004	21.15% (n=375)	13.27% (n=R55 747.86)	0	0	78.85% (n=1398)	86.73% (n=R364 467.45)	0	0
Jan-Apr 2005	17.05% (n=170)	9.38% (n=R24 354.84)	0	0	82.95% (n=827)	90.62% (n=R235 167.79)	0	0
May-Aug 2005	18.95% (n=206)	10.87% (n=R30 383.67)	0	0	81.05% (n=881)	89.13% (n=R249 259.89)	0	0
Sept-Dec 2005	20.67% (n=203)	11.70% (n=R29 683.07)	0	0	79.33% (n=779)	88.30% (n=R224 007.30)	0	0
Jan-Apr 2006	12.48% (n=76)	6.76% (n=R1 181.10)	0	0	87.52% (n=533)	93.01% (n=R163 521.42)	0	0
May-Aug 2006	13.14% (n=77)	7.35% (n=R12 359.11)	0	0	86.86% (n=509)	92.65% (n=R155 818.59)	0	0
Sept-Dec 2006	14.89% (n=81)	8.37% (n=R13 013.43)	0	0	85.11% (n=463)	91.63% (n=R142 517.75)	0	0

*%= Total prevalence or cost of all single item innovators or generics or combination innovators or generics

Total prevalence or cost of all trandolapril containing medicine items

TRANDOLAPRIL

All the items in this section are either single items innovators or combination item generics (also refer to table 5.18). For prevalence and cost of the individual ACE inhibitor products, refer to Appendix B table B11.

As shown in table 5.18 trandolapril containing single item innovators decreased by 1.99% (n=378) from 2004 until 2005 and decrease further by 5.42% (n=345) from 2005 until 2006. The combination innovator items increased by 9.99% from 2004 until 2005 although the number of items decreased by 1141 and then increased further by 5.42% from 2005 until 2006 although the number of items the decreased further by 982 items. This reduction in the number items and the increase in percentage might be attributed to the decrease in the total trandolapril prevalence from 2004 until 2006 (refer to table 5.18). In addition to this the prevalence percentage of the combination items as well as the number of items was consistently higher than that of the single items.

Table 5.18 also showed that the total cost percentage of all trandolapril items decreased by 2.96% (n=R85 959.90) from 2004 until 2005 for the single items and with 3.19% (n=R47 167.94) from 2005 until 2006. The combination items showed a constant increase in contribution of 2.96% from 2004 until 2005, although the total cost decreased by R372 983.53 and the total cost contribution increased further by 3.19% while the total cost decreased by R246 577.22 from 2005 until 2006.

5.6.2 New ACE inhibitor products on the market

In this section, the new ACE inhibitor products that were recorded on the database are illustrated in table 5.19, according to the period in which they were claimed for the first time and whether they are single items, combination items, innovator items or generic items. In each of the study periods, the previous period was used as the basis period.

Table 5.19: New ACE inhibitor products recorded on the database from 2004-2006

Active ingredient	Period	Tradename	Single item		Combination item	
			Innovator	Generic	Innovator	Generic
Benazepril	2004	None				
	2005	None				
	2006	None				
Captopril	2004	Merck-Captopril® 50mg		√		
		Captoretic® 25/12.5mg				√
	2005	Aceten®		√		
	2006	None				
Cilazapril	2004	None				
	2005	None				
	2006	None				
Enalapril	2004	Ciplatec® 20mg		√		
	2005	None				
	2006	None				
Fosinopril	2004	None				
	2005	None				
	2006	Merck-Fosinopril® 10mg		√		
		Merck-Fosinopril® 20mg		√		
Lisinopril	2004	Zetomax® 20mg		√		
		Zetomax® 10mg		√		
		Zetomax® 5mg		√		
		Sinopren® 20mg		√		
		Hexal-Lisinopril® 20mg		√		
		Sinopren® 10mg		√		
		Sinopren® 5mg		√		
		Zemax® 10mg		√		
		Renotens® 5mg		√		
	2005	Zemax® 5mg		√		
		Austell-Lisinopril® 20mg		√		
	2006	Zemax® 20mg		√		
Moexipril	2004	None				
	2005	None				
	2006	None				
Perindopril	2004	Prexum®		√		
		Preterax®			√	
	2005	Bipreterax®				√
	2006	Coversyl® 10mg	√			
		Prexum Plus®			√	
Quinapril	2004	None				
	2005	None				
	2006	Quinaspen® 20mg		√		
		Quinaspen® 10mg		√		
		Adco-Quinaretic® 20/12.5mg				√
		Adco-Quinaretic® 10/12.5mg				√

Table 5.19 (continued): New ACE inhibitor products recorded on the database from 2004-2006

Active ingredient	Period	Tradename	Single item		Combination item	
			Innovator	Generic	Innovator	Generic
Ramipril	2004	Ramace® 2.5mg cap.	√			
		Tritace 'Z ® 1.25mg	√			
		Ramace® 5mg tab.		√		
		Tritace® comb. 2.5/5mg			√	
	2005	Ramiwin® 5mg		√		
		Ramiwin® 2.5mg		√		
		Ramipril-Hexal® 5mg		√		
		Ramipril-Hexal® 2.5mg		√		
		Ramiwin® 1.25mg		√		
		Ramipril-Hexal® 1.25mg		√		
	2006	Ran-Ramipril®		√		
		Rampil® 2.5mg		√		
		Rampil® 10mg		√		
		Rampil® 5mg		√		
		Rampil® 1.25mg		√		
		Austell-Ramipril® 10mg		√		
Trandolapril	2004	None				
	2005	None				
	2006	None				

It can be concluded from table 5.19 that of all the new trade names only 6.98% (n=3) of the trade names were single item innovators, 76.74% (n=33) of the trade names were single item generics, 6.98% (n=3) were combination item innovators and 9.30% (n=4) were combination item generics. The fact that there were more generic products by 2006, increased the choices of using different generic products.

5.7 Combinations of ACE inhibitors and other antihypertensive products per prescription

5.7.1 Introduction

In this section the ACE inhibitors prescribed together with other antihypertensive products on one prescription claimed through Interpharm® Datasystem are discussed.

The benefits of prescribing an ACE inhibitor together with a β–blocker are illustrated in chapter 2, section 2.3.6.4.

The benefits of prescribing an ACE inhibitor together with an angiotensin antagonist (ARB) are illustrated in chapter 2, section 2.3.6.2.

The benefits of prescribing an ACE inhibitor together with calcium-channel blocker (CCB) are illustrated in chapter 2, section 2.3.6.1.

The benefits of prescribing an ACE inhibitor together with a diuretic are illustrated in chapter 2, section 2.3.6.3.

Although the combinations of an ACE inhibitor prescribed together with a diuretic are not discussed in this section, these two items are in fixed combination (refer to appendix B for the products in combination with hydrochlorothiazide (HCTZ)).

- **Two combination**

The two combination consists of a prescription containing an ACE inhibitor and either a β-blocker, an angiotensin antagonist, a calcium-channel blocker, another ACE inhibitor or other antihypertensive products (such as diuretics, vasodilators etc.) (also refer to Appendix C, table C1 to C4 for individual product combinations) .

Table 5.20: ACE inhibitor(s) prescribed together with one other antihypertensive item from 2001-2006

Period	ACE inhibitor/ β blocker	ACE inhibitor/ ARB's	ACE inhibitor/ CCB's	ACE inhibitor/ ACE inhibitor
2001-2002	4.35%* (n=613)	1.80%* (n=253)	12.98%* (n=1828)	5.16%* (n=727)
2004	4.92%* (n=630)	2.57%* (n=329)	14.82%* (n=1899)	4.86%* (n=623)
2005	4.56%* (n=315)	2.46%* (n=170)	24.28%* (n=1677)	3.58%* (n=247)
2006	2.95%* (n=97)	3.53%* (n=116)	43.32%* (n=1424)	4.35%* (n=143)

ARB: Angiotensin receptor blockers (Angiotensin antagonists)

CCB: Calcium channel blocker

*%= Total prevalence of an ACE inhibitor prescribed together with either a β blocker/ ARB/CCB or another ACE inhibitor / Total prevalence of all combinations containing at least one ACE inhibitor

According to table 5.20 the number prescriptions containing β-blockers with ACE inhibitors decreased by 0.36% from 2004 until 2005 and then decreased even further by 1.61% from 2005 until 2006. The angiotensin antagonists prescribed together with an ACE inhibitor showed a decrease of 0.11% from 2004 until 2005 and then increased by 1.07% for 2005 until 2006.

The fact that the percentage increased while the number of items decreased might be attributed to the decrease in the total number of all antihypertensive items prescribed together with ACE inhibitors decreased.

Table 5.20 also shows that the prescriptions containing calcium channel blockers with ACE inhibitors increased by 9.46% from 2004 until 2005 and then increased further by 19.04% from 2005 until 2006. In addition to this the number of times ACE inhibitors were prescribed together with other ACE inhibitors on the same prescription decreased by 1.28% from 2004 until 2005 and then increased by 0.77% from 2005 until 2006.

It can be concluded from table 5.20 that only the combination with calcium-channel blockers showed an increase in percentage from 2004 until 2006. This increase might be attributed to the potential benefits of combining ACE inhibitors with calcium-channel blockers (also refer to chapter 2, section 2.3.6.1).

- **Three combination**

The three combination consists of a prescription containing an ACE inhibitor and either a β–blocker, and/or angiotensin antagonist, and/or calcium-channel blocker and/or another ACE inhibitor or other antihypertensive products (such as diuretics, vasodilators etc.) (also refer to Appendix C, table C5 to C8 for individual product combinations).

Table 5.21: ACE inhibitor(s) prescribed together with two other antihypertensive items from 2001-2006

Period	ACE inhibitor/β-blocker /1 antihypertensive item	ACE inhibitor/ ARB's/ 1 antihypertensive item	ACE inhibitor/calcium CCB's/ 1 antihypertensive item	ACE inhibitor/ACE inhibitors/1 antihypertensive item
2001-2002	12.14%* (n=178)	4.64%* (n=68)	26.47%* (n=388)	9.75%* (n=143)
2004	13.88%* (n=203)	3.55%* (n=52)	24.27%* (n=355)	7.31%* (n=107)
2005	10.72%* (n=83)	5.43%* (n=42)	25.58%* (n=198)	10.21%* (n=79)
2006	7.30%* (n=17)	15.45%* (n=36)	55.79%* (n=130)	8.58%* (n=20)

ARB: Angiotensin receptor blockers (Angiotensin antagonists)

CCB: Calcium channel blocker

*%= Total prevalence of an ACE inhibitor prescribed together with either a β blocker/ ARB/CCB or another ACE inhibitor / Total prevalence of all combinations containing at least one ACE inhibitor

Table 5.21 shows that prescriptions containing an ACE inhibitor, a β-blockers and one other antihypertensive item decreased by 3.16% (n=120) from 2004 until 2005 and then decreased further by 3.42% from 2005 until 2006. Furthermore, the ACE inhibitor prescribed together with an angiotensin antagonist and one other antihypertensive item increased by 1.88% from 2004 until 2005 and then increased by 10.02% from 2005 until 2006. In addition to this, prescriptions containing an ACE inhibitor, a calcium-channel blocker and one other antihypertensive item showed an increase in prevalence percentage of 1.31% from 2004 until 2005 and then increased further by 30.21% from 2005 until 2006. Prescriptions with ACE inhibitors prescribed together with other ACE inhibitors and one other antihypertensive item showed an increase in prevalence percentage of 2.90% although the number of times it was prescribed decreased by 1.63% from 2005 until 2006.

It can be concluded from table 5.21 that ACE inhibitors prescribed together with the calcium-channel blockers and one other antihypertensive item showed higher contributions than ACE inhibitor combinations with angiotensin antagonists or β-blockers with and one other antihypertensive item (refer to chapter 2, section 2.3.6.1. for reasons of using calcium-channel blockers together with ACE inhibitors).

- **Four combination**

The four combination consists of a prescription containing an ACE inhibitor and either a β–blocker, and/or angiotensin antagonist, and/or calcium-channel blocker and/or another ACE inhibitor or other antihypertensive products (such as diuretics, vasodilators etc.) (Also refer to appendix C, table C9 to C12 for individual product combinations).

Table 5.22: ACE inhibitor(s) prescribed together with three other antihypertensive items from 2001-2006

Period	ACE inhibitor/β-blocker /2 antihypertensive items	ACE inhibitor/ ARB's/ 2 antihypertensive items	ACE inhibitor/ CCB's/ 2 antihypertensive items	ACE inhibitor/ACE inhibitor/2 antihypertensive items
2001-2002	0	0	0	0
2004	34.42%* (n=53)	3.25%* (n=5)	24.03%* (n=37)	14.29%* (n=22)
2005	17.86%* (n=10)	3.57%* (n=2)	32.14%* (n=18)	23.21%* (n=13)
2006	11.11%* (n=1)	0	22.22%* (n=2)	0

ARB: Angiotensin receptor blockers (Angiotensin antagonists)

CCB: Calcium channel blocker

*%= Total prevalence of an ACE inhibitor prescribed together with either a β blocker/ ARB/CCB or another ACE inhibitor

Total prevalence of all combinations containing at least one ACE inhibitor

According to table 5.22 prescriptions containing an ACE inhibitor with a β-blocker and two other antihypertensive items decreased by 16.56% from 2004 until 2005 and then decreased further by 6.75% from 2005 until 2006. Prescriptions containing angiotensin antagonists and ACE inhibitor and two other antihypertensive items showed an increase of 0.32% from 2004 until 2005 and then decreased to zero from 2005 until 2006.

Table 5.22 further shows that the number of times an ACE inhibitor and a calcium-channel blocker and two other antihypertensive item were prescribed together increased by 8.11% from 2004 until 2005 and then decreased by 9.92% from 2005 until 2006. In addition to this the number of times an ACE inhibitor was prescribed together with another ACE inhibitor and two other antihypertensive items increased by 8.92% from 2004 until 2005 and then decreased to zero from 2005 until 2006.

It can be concluded from table 5.22 that the combinations with calcium channel blockers were prescribed more than the other combinations with ACE inhibitors.

- **Five combination**

The five combination consists of a prescription containing an ACE inhibitor and either a β–blocker, and/or angiotensin antagonist, and/or calcium-channel blocker and/or another ACE inhibitor or other antihypertensive products (such as diuretics, vasodilators etc.)(also refer to Appendix C, table C13 and C14 for individual product combinations).

Table 5.23: ACE inhibitor(s) prescribed together with four other antihypertensive items from 2001-2006

Period	ACE inhibitor/β-blockers /3 antihypertensive items	ACE inhibitor/ ARB's /3 antihypertensive items	ACE inhibitor/ CCB's/ 3 antihypertensive items	ACE inhibitor/ACE inhibitors/3 antihypertensive items
2001-2002	0	0	100%* (n =18)	0
2004	31.03%* (n=9)	17.24%* (n=5)	55.17%* (n=16)	6.90%* (n=2)
2005	0	0	0	0
2006	0	0	0	0

ARB: Angiotensin receptor blockers (Angiotensin antagonists)

CCB: Calcium channel blocker

*%= Total prevalence of an ACE inhibitor prescribed together with either a β blocker/ ARB/CCB or another ACE inhibitor

Total prevalence of all combinations containing at least one ACE inhibitor

It can be concluded from table 5.23 that the prescriptions containing ACE inhibitors and β-blockers and three other antihypertensive items or angiotensin antagonists or calcium-channel blockers and three other antihypertensive items or other ACE inhibitors with three other antihypertensive products showed decreases of 31.03%, 17.24%, 55.17% and 6.90% respectively to zero percent from 2004 until 2005. For the period of 2005 until 2006 a prevalence of zero was also shown. Furthermore, it can be added that the calcium-channel blocker combinations were prescribed more than the other combinations, and this might again be attributed to the benefits of using these combinations of ACE inhibitors and calcium channel blockers (refer to chapter 2, section 2.3.6.1). ACE inhibitors prescribed together with calcium-channel blockers and three other antihypertensive item were prescribed together more throughout 2001-2006 than any other combination of ACE inhibitor and antihypertensive item.

- **Six combination**

The six combination consists of a prescription containing an ACE inhibitor and either a β–blocker, and/or angiotensin antagonist, and/or calcium-channel blocker and/or another ACE inhibitor or other antihypertensive products (such as diuretics, vasodilators etc.) (also refer to appendix C, table C15).

Table 5.24: ACE inhibitor(s) prescribed together with five other antihypertensive items from 2001-2006

Period	ACE inhibito/β-blockers /4 antihypertensive items	ACE inhibitor/ ARB's /4 antihypertensive items	ACE inhibitor/ CCB's/ 4 antihypertensive items	ACE inhibitor/ACE inhibitors/4 antihypertensive items
2001-2002	0	0	0	0
2004	0	0	0	0
2005	0	0	0	0
2006	0	0	0	0

ARB: Angiotensin receptor blockers (Angiotensin antagonists)

CCB: Calcium channel blocker

*%= Total prevalence of an ACE inhibitor prescribed together with either a β blocker/ ARB/CCB or another ACE inhibitor

Total prevalence of all combinations containing at least one ACE inhibitor

It can be concluded from table 5.24 that there were no combinations containing ACE inhibitors and β-blockers and four other antihypertensive items or angiotensin antagonists and four other antihypertensive item or calcium-channel blockers and four other antihypertensive item or other ACE inhibitors and together with four other antihypertensive products from 2001-2006, but the year 2004 did show a combination of six antihypertensive products, one of which is an ACE inhibitor and does not contain an angiotensin antagonist, calcium channel blocker or another ACE inhibitor as combination (refer to appendix C, table C15).

The results reveal that sometimes the same active ingredients were prescribed together. The possible explanation for this might be:

- That two different products with the same active ingredient in different strengths were prescribed together
- The correct packaging of the product was not available and a larger packaging had to be opened.

5.8 Number of prescriptions per patient containing at least one ACE inhibitor

5.8.1 Introduction

In this section the number of prescriptions per patient containing at least one ACE inhibitor will be discussed from 2001-2002, 2004, 2005, 2006. The numbers of patients and prescriptions are summarised in table 5.25 to 5.28.

Table 5.25: Number of prescriptions per patient containing at least one ACE inhibitor from 2001-2006

Period	Number of patients (N)	Average number of prescriptions	Standard deviation (±)	Number of prescriptions (N)
2001-2002	42303	4.67	4.16	197 765.00
2004	41303	4.43	3.36	182 970.00
2005	21351	4.92	3.84	105 117.00
2006	13506	4.12	3.48	55 667.00

It can be concluded from table 5.25 that the number of patients receiving at least one ACE inhibitor prescription decreased by 48.31% (n=19952) from 2004 until 2005. The number of prescriptions decreased by 42.55% (n=77853) from 2004 until 2005 and the number of patients then decrease further by 36.74% (n=7845). The number of prescriptions decreased further by 47.04% (n=49450) from 2005 until 2006. The fact that the average number of prescriptions per patient increased from 2004 until 2005, indicates that a patient received more prescriptions containing ACE inhibitors. The reduction in the number of patients might be a result of the reduction in the number of medical schemes, number of medical scheme dependants and number of prescriptions.

Table 5.26: **Frequency of the total number of prescriptions per patient containing at least one ACE inhibitor for 2001-2002**

Total prescriptions	Number of patients	Patient percentage	Cumulative patient percentage
1	11962	28.28%	28.28%
2	7487	17.70%	45.98%
3	3881	9.17%	55.15%
4	2896	6.85%	62.00%
5	2373	5.61%	67.61%
6	1800	4.26%	71.86%
7	1629	3.85%	75.71%
8	1522	3.60%	79.31%
9	1549	3.66%	82.97%
10	1678	3.97%	86.94%
11	1837	4.34%	91.28%
12	1805	4.27%	95.55%

According to table 5.26 only 28.28% (n=11962) of the patients claimed one prescription per year containing at least one ACE inhibitor and 4.27% (n=1805) of patients claimed twelve prescriptions per year i.e. one per month for ACE inhibitors which are chronic medication and should be taken on a daily and monthly basis. However if all of the patients were compliant and claimed a prescription every month then the majority of the patients would be in the category where the twelve prescriptions were claimed.

In addition to this and for the duration of this study it was determined that any patient compliance below 80% (below nine prescriptions per year) was regarded as non-compliant. Therefore 16.24% (n=6869) of patients claimed 80% or more of their twelve month prescriptions and 4.27% of the patients received twelve prescriptions, an average of one per month. The results reveal that 4.45% of the patients received more than twelve prescriptions per year.

From the literature it seems that many patients who are non-compliant taking their medication also do not realise what adverse outcomes they are to experience (also refer to chapter 2, section 2.2.1.18).

Possible causes of patient non-compliance include (Rosner, 2006:558):

- Lack of knowledge about the treatment regimen
- Impact on the patient's lifestyle and need for changes
- Complexity of the treatment and extended duration
- Resource limitations such as no transportation to the clinic or pharmacy
- Lack of awareness of illness and consequences of non-compliance

- Fear of weight gain, forgetfulness, indifference
- Feeling of doubt, vulnerability and side-effects.

Other causes include: patients being given a small amount of ACE inhibitor tablets to see what the patient response is to the tablets and then changing the medication. This would lead to an increase in claims for ACE inhibitor products and therefore have negative influences on compliance figures calculated from the medicine claims database.

There might also be other reasons for non-compliance, but these are not included in this study and warrant further investigation.

Possible adverse outcomes related to non-compliance include (Rosner, 2006:558):

- Worsening or aggravation of the illness
- Decreased quality of life
- Additional diagnostic testing
- Added discomfort to the patient
- Increased costs to the patient and health care system
- Deterioration of physician-patient relationship
- Adverse effects on the patient's health.

Table 5.27: Frequency of the total number of prescriptions per patient containing at least one ACE inhibitor for 2004

Total prescriptions	Number of patients	Patient percentage	Cumulative patient percentage
1	10717	25.95%	25.95%
2	5610	13.58%	39.53%
3	4674	11.32%	50.85%
4	3932	9.52%	60.37%
5	2662	6.45%	66.81%
6	2436	5.90%	72.71%
7	2356	5.70%	78.41%
8	2514	6.09%	84.50%
9	2087	5.05%	89.55%
10	1388	3.36%	92.91%
11	1458	3.53%	96.44%
12	1131	2.74%	99.18%

As shown in table 5.27, 25.95% (n=10717) of patients claimed one prescription containing at least one ACE inhibitor and 2.74% (n=1131) of patients claimed twelve prescriptions per year.

Table 5.27 also reveals that 14.68% (n=6064) of patients claimed 80% or more of their twelve month prescriptions and 2.74% of the patients received twelve prescriptions, an average of one per month. Thus, 0.82% of the patients received more than twelve prescriptions per year.

Table 5.28: Frequency of the total number of prescriptions per patient containing at least one ACE inhibitor for 2005

Total prescriptions	Number of patients	Patient percentage	Cumulative patient percentage
1	5778	27.06%	27.06%
2	2711	12.70%	39.76%
3	1943	9.10%	48.86%
4	1433	6.71%	55.57%
5	1269	5.94%	61.51%
6	1213	5.68%	67.20%
7	1084	5.08%	72.27%
8	1064	4.98%	77.26%
9	1008	4.72%	81.98%
10	987	4.62%	86.60%
11	1195	5.60%	92.20%
12	1195	5.60%	97.79%

According to table 5.28, 27.06% (n=5778) of patients claimed one prescription containing an ACE inhibitor for 2005. The number of patients who claimed on one prescription therefore decreased by 15 892 from 2004 and the patient percentage increased by 1.11% from 2004. Table 5.28 further reveals that 20.54%(n=4385) of patients claimed 80% of their prescriptions during 2006. The number of patients claiming twelve prescriptions increased by 64 from 2004 until 2005 and the patient percentage increased by 2.86% from 2004 until 2005. The total number of patients who received twelve prescriptions or less decreased by 1.39% from 2004 and the number of patients who received more than twelve prescriptions increased by 1.39% from 2004.

Table 5.29: Frequency of the total number of prescriptions per patient containing at least one ACE inhibitor for 2006

Total prescriptions	Number of patients	Patient percentage	Cumulative patient percentage
1	4387	32.48%	32.48%
2	1988	14.72%	47.20%
3	1367	10.12%	57.32%
4	1047	7.75%	65.07%
5	800	5.92%	71.00%
6	665	4.92%	75.92%
7	601	4.45%	80.37%
8	547	4.05%	84.42%
9	504	3.73%	88.15%
10	504	3.73%	91.89%
11	467	3.46%	95.34%
12	500	3.70%	99.04%

As shown in table 5.29, 32.48% (n=4387) of the patients claimed one prescription that contained at least one ACE inhibitor for 2006. Although the percentage increased, the number of patients who received one prescription decreased by 1391 from 2005. The number of patients that received twelve prescriptions decreased by 1.90% (n=695) from 2005 until 2006. Table 5.29 further reveals that 14.62% (n=1975) of patients claimed 80% of their prescriptions during 2006. The total number of patients that received twelve prescriptions or less decreased by 1.25% from 2005 and the number of patients that received more than twelve prescriptions increased by 1.25% from 2005.

It can be concluded from section 5.8 that the number of patients claiming less than twelve prescriptions per year decreased constantly from 2004 until 2006. The percentage of patients claiming one prescription per year containing at least one ACE inhibitor increased constantly from 2004 until 2006 although the number of patients decreased constantly. The percentage of patients who claimed twelve prescriptions or less per year decreased from 2004 until 2005 and then increased from 2005 until 2006. Furthermore, the number of patients claiming more than twelve prescriptions per year containing at least one ACE inhibitor increased from 2004 until 2005 and then decreased from 2005 until 2006.The number of patients that were deemed compliant (claiming 80% or more of their prescriptions) showed a constant decrease from 2004 until 2006.

It can further be concluded that patient compliance in the use of ACE inhibitors was a problem from 2004 until 2006 and a greater effort must be made to improve the compliance and therefore benefit the patient. Possible solutions to increase patient compliance are listed below.

Possible solutions to the problem of patient non-compliance with treatment regimen are to (Rosner, 2006:558):

- Provide the patient with better education (also refer to chapter 2, section 2.2.1.16)
- Motivate patients to comply – give reasons for the need to comply
- Provide effective communication between patient and caregiver
- Reduce complexity of medication regimens.

The complexity of medication regimens can be reduced by using combination medicine items (refer to chapter 2, section 2.3.3).

5.9 Prescribed daily dose and effect sizes of the ACE inhibitor active ingredient innovators and generics.

5.9.1 Introduction

In this section the prescribed daily dose (PDD) is determined between the innovator and generic items of each active ingredient (also refer to chapter 3, section 3.2.8.2). The effect sizes (d-values) calculated between the average cost of the innovator and generic items of each active ingredient are also discussed. Note that in the case where a "—" is indicated in the effect size column, there was no innovator and/or generic available for the respective active ingredient and the effect size could not be determined. The effect sizes in table 5.30 and 5.31 were calculated from the data in table 5.32 and the effect sizes in table 5.33 and 5.34 were calculated from the data in table 5.35. Although all of the PDDs of all the active ingredients were determined, only the ones with an innovator as well as a generic are discussed from table 5.30 to 5.31 and 5.33 to 5.34. The PDDs in table 5.30, 5.31, 5.33 and 5.34 were calculated by dividing the mean by the median and dividing it by the strength of the individual active ingredient. The median represents the number of days for which up to 50% of the patient population received the relevant medicine item (active ingredient and strength). The mean represents the average number of tablets per prescription for each of the active ingredients as well as their respective strengths.

Table 5.30: Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2001-2002

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Quinapril 5mg	1316[&]	29.25	7.65	28.52	5.13mg^	—
Quinapril 10mg	4375[&]	29.45	5.26	28.52	10.32mg^	—
Quinapril 20mg	2905[&]	29.16	4.13	28.52	20.15mg[?]	—
Quinapril 40mg	358[&]	27.44	6.65	28.52	38.48mg[?]	—
Quinapril/HCTZ 10/12.5mg	6974[&]	28.72	3.48	28.52	10.07/12.41mg[$]	—
Quinapril/HCTZ 20/12.5mg	8865[&]	28.69	3.25	28.52	20.12/12.43mg[$]	—
Captopril 12.5mg	325[&]	54.98	29.87	28.52	12.04mg[∂^]	0.84
	489[@]	52.54	20.72	28.52	11.51mg[∂^]	
Captopril 25mg	875[&]	55.55	27.60	28.52	24.35mg[∂!]	1.13
	4565[@]	56.98	25.03	28.52	24.98mg[∂!]	
Captopril 50mg	682[&]	60.70	20.21	28.52	53.20mg[∂$]	1.74
	1901[@]	60.75	19.75	28.52	53.25mg[∂$]	
Enalapril 5mg	2856[&]	30.97	9.38	28.52	5.43mg^	0.40
	2009[@]	31.53	8.81	28.52	5.52mg^	
Enalapril 10mg	4837[&]	31.20	8.58	28.52	10.94mg^	0.55
	8023[@]	31.87	9.35	28.52	11.17mg^	
Enalapril 20mg	4802[&]	29.48	5.51	28.52	20.67mg[!]	0.72
	6989[@]	31.47	7.76	28.52	22.07mg[$]	
Lisinopril 2.5mg	0.00	0.00	0.00	0.00	0.00	—
Lisinopril 5mg	1165[&]	29.69	5.08	28.52	5.20mg^	1.22
	2646[@]	30.44	5.75	28.52	5.34mg^	
Lisinopril 10mg	2530[&]	29.89	2.23	28.52	10.48mg^	1.66
	6588[@]	30.17	3.92	28.52	10.58mg^	
Lisinopril 20mg	1964[&]	30.62	5.05	28.52	21.46mg[?]	1.24
	5797[@]	30.54	5.08	28.52	21.42mg[?]	
Ramipril 1.25mg	1118[&]	32.10	8.53	28.52	1.41mg^	—
Ramipril 2.5mg	8286[&]	31.63	8.13	28.52	2.77mg^	—
Ramipril 5mg	9991[&]	32.69	9.60	28.52	5.73mg[?]	—
Ramipril 10mg	3293[&]	30.19	3.55	28.52	10.58mg[$]	—
Indapamide/perindopril 2/0.625mg	0.00	0.00	0.00	0.00	0.00	—
Indapamide/perindopril 4/1.25mg	12378[&]	30.12	3.46	28.52	4.22/1.18mg[!]	—
Captopril/HCTZ 25/12.5mg	121[&]	32.88	9.05	28.52	28.82/10.84mg[?]	—
Captopril/HCTZ 50/25mg	477[&]	30.65	7.58	28.52	53.73/23.26mg[?]	1.23
	2029[@]	30.83	9.17	28.52	54.06/23.12mg[?]	
Benazepril 5mg	36[&]	31.86	9.42	28.52	5.59mg^	—
Benazepril 10mg	275[&]	30.07	3.10	28.52	10.54mg^	—
Benazepril 20mg	76[&]	30.39	3.44	28.52	21.32mg[?]	—
Benazepril/HCTZ 10/12.5mg	280[&]	28.88	4.53	28.52	10.12/12.35mg[?]	—
Enalapril/HCTZ 20/12.5mg	8295[&]	28.47	3.48	28.52	19.97/12.52mg[!]	0.91
	4094[@]	29.86	4.91	28.52	20.94/11.94mg[?]	

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter4, section 4.8.2.6)

[&] (Innovator) / [@] (Generic).

Table 5.30 (continued): Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2001-2002

Active ingredient	Frequency (N)	Quantity tabs. Or caps. Per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Perindopril 4mg	30031[&]	30.10	7.51	28.52	4.22mg[?]	—
Perindopril 10mg	0.00	0.00	0.00	0.00	0.00	—
Lisinopril/HCTZ 10/12.5mg	5348[&]	30.01	3.11	28.52	10.32/11.88mg[?]	—
Lisinopril/HCTZ 20/12.5mg	9023[&]	30.21	3.50	28.52	21.18/11.80mg[?]	—
Cilazapril 2.5mg	954[&]	28.48	5.60	28.52	2.50mg[?]	—
Cilazapril 5mg	632[&]	28.61	2.95	28.52	5.02mg[!]	—
Cilazapril/HCTZ 5/12.5mg	1225[&]	28.85	3.03	28.52	5.06/12.36mg[!]	—
Trandolapril 0.5mg	121[@]	34.21	10.47	28.52	0.60mg^	—
Trandolapril 2mg	1561[&]	33.84	11.55	28.52	2.37mg^	—
Fosinopril 10mg	1512[&]	31.41	7.40	28.52	11.01mg^	—
Fosinopril 20mg	835[&]	3.54	4.89	28.52	21.42mg[?]	—
Fosinopril/HCTZ 20/12.5mg	1025[&]	30.12	4.43	28.52	21.12/11.84mg[$]	—
Moexipril 7.5mg	9[&]	30	0.00	28.52	7.89mg[?]	—
Moexipril 15mg	0.00	0.00	0.00	0.00	0.00	—
Verapamil/Trandolapril 180/2mg	4160[&]	30.90	6.00	28.52	195/1.85mg[$]	—
Ramipril/Felodipine 2.5/2.5mg	2071[&]	30.14	3.68	28.52	2.64/2.64mg[!]	—
Ramipril/Felodipine 5/5mg	2984[&]	30.14	3.31	28.52	5.28/5.28mg[!]	—
Enalapril 2.5mg	520[&]	31.97	10.50	28.52	2.80mg^	0.31
	90[@]	35.93	12.11	28.52	3.15mg^	
Lisinopril/HCTZ 20/25mg	0.00	0.00	0.00	0.00	0.00	—
Enalapril 5mg	122[@]	32.65	11.05	28.52	5.72mg^	—
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00	0.00	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients. (refer to chapter 4, section 4.8.2.6)

[&] (Innovator) / [@] (Generic).

According to table 5.30 the PDD established for an innovator as well as a generic and the lowest difference in PDD of 0.05mg/day between innovator and generic was by captopril 50mg and the highest difference was for enalapril 20mg of 1.40mg/day.

As shown in table 5.30 the item for this period with the highest effect size was captopril 50mg with 1.74 and of practical significance (refer to chapter 4, section 4.8.2.5), the lowest effect size was for enalapril 2.5mg with 0.31 and therefore of no practical significance. Furthermore, of all

the effect sizes, 66.67% (n=8 active ingredients) had effect sizes of practical significance between innovator and generic.

The following are applicable to table 5.30.

[?] The prescribed daily dose (PDD) of the active ingredient and strength falls within the minimum and maximum maintenance dose range according to the MIMS®. Only seventeen (27.87%) active ACE inhibitor ingredients including different strengths fall within this range.

[!] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% of the minimum and maximum maintenance dose range according to the MIMS®. Only nine (14.75%) active ACE inhibitor ingredients including different strengths fall with this range.

[$] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% -10% of the minimum and maximum maintenance dose range according to the MIMS®. Only four (6.56%) active ACE inhibitor ingredients including different strengths fall within this range.

[^] The prescribed daily dose (PDD) of the active ingredient and strength falls outside 10% of the minimum and maximum maintenance dose range according to the MIMS® and the remaining thirty one (50.82%) active ACE inhibitor ingredients including strengths fall within this range.

In many of the active ingredient dosages falling outside the dosage range of the MIMS® it might be that some of these dosages were used as initial and not as maintenance dosages.

Table 5.31: Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2004

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Quinapril 5mg	649[&]	29.64	6.58	29.83	4.97mg^	—
Quinapril 10mg	2422[&]	29.13	4.91	29.83	9.76mg^	—
Quinapril 20mg	1923[&]	29.74	5.85	29.83	19.94mg[!]	—
Quinapril 40mg	536[&]	27.27	5.91	29.83	36.57mg[?]	—
Quinapril/HCTZ 10/12.5mg	4470[&]	29.18	4.98	29.83	9.78/ 12.78mg[!]	—
Quinapril/HCTZ 20/12.5mg	6679[&]	29.08	3.76	29.83	19.50/ 12.82mg^	—
Captopril 12.5mg	65[&]	48.92	27.99	29.83	20.50mg^	0.45
	432[@]	52.37	23.20	29.83	10.97mg[∂]^	
Captopril 25mg	225[&]	55.13	28.21	29.83	23.10mg[∂$]	0.91
	3672[@]	58.14	24.90	29.83	24.36mg[∂$]	
Captopril 50mg	126[&]	50.90	20.86	29.83	42.66mg[∂?]	0.86
	1510[@]	59.87	19.28	29.83	50.18mg[∂!]	
Enalapril 5mg	1836[&]	31.36	9.81	29.83	5.26mg[∂]^	0.03
	2038[@]	32.90	10.25	29.83	5.51mg^	
Enalapril 10mg	2357[&]	32.11	11.60	29.83	9.29mg^	0.52
	9270[@]	32.10	9.41	29.83	9.29mg^	
Enalapril 20mg	2720[&]	30.58	7.98	29.83	20.50mg[!]	0.48
	7616[@]	30.89	6.51	29.83	20.71mg[!]	
Lisinopril 2.5mg	0.00	0.00	0.00	0.00	0.00	—
Lisinopril 5mg	447[&]	30.10	9.41	29.83	5.04mg^	0.80
	2499[@]	30.20	5.35	29.83	5.06mg^	
Lisinopril 10mg	890[&]	29.85	4.69	29.83	10.01mg^	0.70
	5931[@]	30.02	3.91	29.83	10.06mg^	
Lisinopril 20mg	888[&]	29.95	6.38	29.83	20.08mg[?]	0.54
	6316[@]	30.08	4.64	29.83	20.17mg[?]	
Ramipril 1.25mg	555[&]	31.98	8.65	29.83	1.34mg^	—
Ramipril 2.5mg	5053[&]	30.96	6.93	29.83	2.60mg^	—
Ramipril 5mg	5837[&]	32.07	10.55	29.83	5.38mg[?]	0.45
	628[@]	34.32	10.79	29.33	5.72mg[?]	
Ramipril 10mg	4520[&]	30.33	4.36	29.83	10.17mg[!]	—
Indapamide/perindopril 2/0.625mg	1411[&]	30.23	3.80	29.83	2.03mg^	—
Indapamide/perindopril 4/1.25mg	25926[&]	30.17	3.71	29.83	4.05mg[!]	—
Captopril/HCTZ 25/12.5mg	241[@]	31.73	9.41	29.83	26.59/ 11.75mg^	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter 4, section 4.8.2.6)

[&] (Innovator) / [@] (Generic).

Table 5.31 (continued): Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2004

Active ingredient	Frequency (N)	Quantity tabs. Or caps. Per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Captopril/HCTZ 50/25mg	285[&]	39.95	19.01	29.83	66.96/ 18.67mg[?]	1.40
	1699[@]	32.49	11.98	29.83	54.46/ 22.95mg[?]	
Benazepril 5mg	68[&]	28.46	4.59	29.83	4.77mg^	—
Benazepril 10mg	213[&]	30.00	0.00	29.83	10.06mg^	—
Benazepril 20mg	87[&]	30.00	0.00	29.83	20.14mg[?]	—
Benazepril/HCTZ 10/12.5mg	209[&]	29.09	4.37	29.83	9.75/ 12.82mg[!]	—
Enalapril/HCTZ 20/12.5mg	4757[&]	29.11	8.07	29.83	19.52/ 12.81mg[!]	0.62
	7846[@]	29.84	4.05	29.83	20.01/ 12.50mg[?]	
Perindopril 4mg	12793[&]	29.94	8.12	29.83	4.02mg[?]	0.45
	20959[@]	30.15	7.14	29.83	4.04mg[?]	
Perindopril 10mg	0.00	0.00	0.00	0.00	0.00	
Lisinopril/HCTZ 10/12.5mg	2976[&]	30.09	4.56	29.83	10.09/ 12.39mg[?]	—
Lisinopril/HCTZ 20/12.5mg	5406[&]	30.38	5.50	29.83	20.37/ 12.27mg[?]	—
Cilazapril 2.5mg	671[&]	29.10	5.68	29.83	2.44mg[$]	—
Cilazapril 5mg	565[&]	29.55	5.31	29.83	4.95mg[?]	—
Cilazapril/HCTZ 5/12.5mg	923[&]	29.26	4.81	29.83	4.90/ 12.74mg[!]	—
Trandolapril 0.5mg	57[&]	30.53	3.97	29.83	0.51mg^	—
Trandolapril 2mg	900[&]	33.59	10.39	29.83	2.25mg^	—
Fosinopril 10mg	844[&]	30.21	4.66	29.83	10.13mg^	—
Fosinopril 20mg	543[&]	32.10	8.13	29.83	21.52mg[?]	—
Fosinopril/HCTZ 20/12.5mg	870[&]	29.85	6.41	29.83	20.01/ 12.50mg[!]	—
Moexipril 7.5mg	536[&]	30.33	3.21	29.83	7.62mg[?]	—
Moexipril 15mg	255[&]	30.00	2.33	29.83	15.08mg[?]	—
Verapamil/Trandolapril 180/2mg	3628[&]	30.56	4.57	29.83 29.83	175.70mg/ 2.05mg[!]	—
Ramipril/Felodipine 2.5/2.5mg	2164[&]	30.13	3.11	29.83	2.53/2.53mg[!]	—
Ramipril/Felodipine 5/5mg	3681[&]	30.49	5.02	29.83	5.11/5.11mg[!]	—
Enalapril 2.5mg	317[&]	30.71	7.85	29.83	2.57mg^	0.63
	139[@]	31.49	9.33	29.83	2.64mg^	
Lisinopril/HCTZ 20/25mg	0.00	0.00	0.00	0.00	0.00	—
Enalapril 5mg	64[@]	32.63	9.52	29.83	5.47mg^	—
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00	0.00	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

According to table 5.31 the PDD established for an innovator as well as a generic and the lowest difference in PDD of 0mg/day between innovator and generic was by enalapril 10mg and the highest difference was by captopril 12.5mg of 9.53mg/day. In addition to this the generic of captopril 12.5mg had a dose of 10.97mg twice daily and the innovator was 20.50mg once daily, if however the 10.97mg was doubled (twice daily dose) then the difference would be only 1.44mg/day. This is also the only active ingredient that showed a difference in dosing frequency between the innovator and generic products.

As shown in table 5.31 the item for this period with the highest effect size was captopril/HCTZ 50/25mg with 1.40 and of practical significance (refer to chapter 4, section 4.8.2.5), the lowest effect size was for enalapril 5mg with 0.03 and therefore of no practical significance. Furthermore, of all the active ingredients 28.57% (n=4) had effect sizes of practical significance between innovator and generic. With regard to the previous period two more active ingredients had effect sizes (d-values) in 2004. Two new active ingredients that showed effect sizes in 2004 with regard to the previous period were perindopril 4mg and ramipril 5mg. This was due to the introduction of generic items.

The following are applicable to table 5.31.

[?] The prescribed daily dose (PDD) of the active ingredient and strength falls within the minimum and maximum maintenance dose range according to the MIMS®. Only eighteen (30.00%) active ACE inhibitor ingredients and strengths fall within this range.

[!] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% of the minimum and maximum maintenance dose range according to the MIMS®. Only fourteen (23.33%) active ACE inhibitor ingredients and strengths fall within this range.

[$] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% -10% of the minimum and maximum maintenance dose range according to the MIMS®. Only three (5.00%) active ACE inhibitor ingredients and strengths fall within this range.

[^] The prescribed daily dose (PDD) of the active ingredient and strength falls outside 10% of the minimum and maximum maintenance dose range according to the MIMS® and the remaining twenty five (41.62%) active ACE inhibitor ingredients and strengths fall within this range.

Many of the active ingredient dosages falling outside the dosage range of the MIMS® might be because some of these dosages were used as initial and not as maintenance dosages.

Table 5.32: Average cost per ACE inhibitor active ingredient innovators and generics for 2001-2002 and 2004

Active ingredient	2001-2002		2004	
	Average cost /item (R)	standard deviation (±)	Average cost /item (R)	standard deviation (±)
Quinapril 5mg	116.04[&]	30.85	111.96[&]	43.29
Quinapril 10mg	163.16[&]	32.75	154.47[&]	41.24
Quinapril 20mg	245.85[&]	42.80	233.59[&]	62.44
Quinapril 40mg	233.03[&]	57.40	215.35[&]	55.35
Quinapril/HCTZ 10/12.5mg	158.48[&]	25.96	160.78[&]	34.65
Quinapril/HCTZ 20/12.5mg	241.12[&]	37.63	234.96[&]	52.03
Captopril 12.5mg	142.41[&]	91.95	61.26[&]	47.61
	65.45[@]	30.91	40.07[@]	23.13
Captopril 25mg	195.98[&]	100.90	140.21[&]	103.44
	82.26[@]	39.19	45.66[@]	34.03
Captopril 50mg	369.95[&]	129.00	213.78[&]	150.59
	145.59[@]	52.57	84.10[@]	54.57
Enalapril 5mg	104.18[&]	42.78	44.46[&]	18.81
	86.92[@]	33.24	45.03[@]	18.08
Enalapril 10mg	143.77[&]	58.71	61.10[&]	23.11
	111.49[@]	38.05	49.14[@]	18.13
Enalapril 20mg	236.83[&]	82.65	110.12[&]	37.88
	177.30[@]	52.23	92.07[@]	36.75
Lisinopril 2.5mg	0.00	0.00	0.00	0.00
Lisinopril 5mg	108.65[&]	24.34	79.85[&]	44.97
	58.38[@]	41.32	43.86[@]	13.18
Lisinopril 10mg	156.91[&]	26.84	99.94[&]	54.05
	112.45[@]	17.73	62.23[@]	15.64
Lisinopril 20mg	265.33[&]	67.66	148.12[&]	93.44
	181.41[@]	33.27	98.11[@]	26.33
Ramipril 1.25mg	147.99[&]	42.97	153.44[&]	60.01
Ramipril 2.5mg	190.45[&]	52.12	183.14[&]	70.59
Ramipril 5mg	282.39[&]	84.72	279.62[&]	109.35
	0.00	0.00	230.71[@]	88.67
Ramipril 10mg	279.70[&]	46.60	285.44[&]	59.00
Indapamide/perindopril 2/0.625mg	0.00	0.00	197.98[&]	31.06
	0.00	0.00	0.00	0.00
Indapamide/perindopril 4/1.25mg	241.99[&]	35.21	210.89[&]	36.24
	0.00	0.00	0.00	0.00
Captopril/HCTZ 25/12.5mg	107.87[&]	29.61	67.95[&]	30.91
Captopril/HCTZ 50/25mg	247.15[&]	75.18	258.43[&]	118.30
	154.45[@]	45.56	92.78[@]	41.74
Benazepril 5mg	140.31[&]	48.10	134.44[&]	23.38
Benazepril 10mg	162.68[&]	17.79	141.26[&]	59.98
Benazepril 20mg	276.29[&]	43.80	261.32[&]	43.80
Benazepril/HCTZ 10/12.5mg	268.77[&]	45.71	284.02[&]	51.95
Enalapril/HCTZ 20/12.5mg	236.87[&]	64.87	118.57[&]	33.26
	177.72[@]	35.91	97.23[@]	34.42
Perindopril 4mg	217.39[&]	52.89	167.92[&]	68.38
	0.00	0.00	137.20[@]	35.76

[&] (Innovator) / [@] (Generic).

Table 5.32 (continued): Average cost per ACE inhibitor active ingredient innovators and generics for 2001-2002 and 2004

Active ingredient	2001-2002		2004	
	Average cost /item (R)	standard deviation (±)	Average cost /item (R)	standard deviation (±)
Perindopril 10mg	0.00	0.00	0.00	0.00
Lisinopril/HCTZ 10/12.5mg	168.01[&]	20.64	153.25[&]	30.23
Lisinopril/HCTZ 20/12.5mg	288.08[&]	35.18	250.53[&]	65.12
Cilazapril 2.5mg	144.72[&]	37.37	150.70[&]	35.14
Cilazapril 5mg	226.94[&]	40.63	196.78[&]	64.24
Cilazapril/HCTZ 5/12.5mg	231.10[&]	42.97	198.18[&]	62.03
Trandolapril 0.5mg	229.09[@]	75.53	133.90[@]	45.26
Trandolapril 2mg	298.60[&]	138.32	180.83[&]	61.63
Fosinopril 10mg	174.86[&]	43.61	173.16[&]	42.76
Fosinopril 20mg	244.70[&]	42.02	247.23[&]	73.50
Fosinopril/HCTZ 20/12.5mg	239.75[&]	40.10	238.48[&]	51.46
Moexipril 7.5mg	124.97[&]	0.93	121.00[&]	14.62
Moexipril 15mg	0.00	0.00	200.50[@]	17.36
Verapamil/Trandolapril 180/2mg	319.37[&]	63.17	298.08[&]	66.37
Ramipril/Felodipine 2.5/2.5mg	195.27[&]	33.47	206.73[&]	39.13
Ramipril/Felodipine 5/5mg	314.70[&]	40.52	317.73[&]	79.48
Enalapril 2.5mg	88.33[&]	30.66	60.14[&]	14.27
	98.94[@]	34.51	49.06[@]	17.56
Lisinopril/HCTZ 20/25mg	0.00	0.00	0.00	0.00
Enalapril 5mg	37.98[@]	22.92	26.25[@]	6.39
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00

[&] (Innovator) / [@] (Generic).

Table 5.33: Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2005

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Quinapril 5mg	169[&]	30.21	6.89	29.76	5.08mg^	—
Quinapril 10mg	800[&]	30.15	12.86	29.76	10.13mg^	—
Quinapril 20mg	793[&]	32.76	11.91	29.76	22.02mg[?]	—
Quinapril 40mg	171[&]	26.49	5.80	29.76	35.60mg[?]	—
Quinapril/HCTZ 10/12.5mg	1860[&]	29.52	6.30	29.76	9.92/ 12.60mg[!]	—
Quinapril/HCTZ 20/12.5mg	3187[&]	29.28	4.49	29.76	19.68/ 12.70mg[?]	—
Captopril 12.5mg	10[&]	25.00	12.23	29.76	10.50mg^	0.39
	77[@]	37.10	18.45	29.76	15.58mg^	
Captopril 25mg	86[&]	63.85	43.03	29.76	26.82mg[∂?]	0.76
	1207[@]	57.27	26.99	29.76	24.05mg[∂!]	
Captopril 50mg	31[&]	39.71	17.39	29.76	66.72mg[∂^]	1.15
	645[@]	59.37	20.96	29.76	49.87mg[∂?]	
Enalapril 5mg	727[&]	32.89	12.52	29.76	4.52mg^	0.36
	1075[@]	31.70	10.24	29.76	5.33mg^	
Enalapril 10mg	1112[&]	35.37	14.95	29.76	11.88mg^	0.45
	4643[@]	33.26	11.19	29.76	11.18mg^	
Enalapril 20mg	906[&]	31.71	9.80	29.76	21.31mg[$]	0.49
	4183[@]	31.53	8.16	29.76	21.19mg[$]	
Lisinopril 2.5mg	0.00	0.00	0.00	0.00	0.00	—
Lisinopril 5mg	186[&]	30.34	10.18	29.76	5.10mg^	0.51
	787[@]	30.32	6.62	29.76	5.09mg^	
Lisinopril 10mg	330[&]	31.45	7.10	29.76	10.57mg^	0.66
	2203[@]	30.32	4.31	29.76	10.19mg^	
Lisinopril 20mg	218[&]	31.33	12.01	29.76	21.06mg[?]	0.36
	2870[@]	30.82	8.42	29.76	20.71mg[?]	
Ramipril 1.25mg	171[&]	32.28	9.35	29.76	1.36mg^	1.75
	29[@]	32.00	7.76	29.76	1.34mg^	
Ramipril 2.5mg	1772[&]	30.99	7.94	29.76	2.60mg^	1.35
	458[@]	32.53	8.96	29.76	2.73mg^	
Ramipril 5mg	1849[&]	33.09	11.73	29.76	5.56mg[?]	0.42
	952[@]	34.75	13.22	29.76	5.84mg[?]	
Ramipril 10mg	1779[&]	31.37	9.91	29.76	10.54mg[$]	—
Indapamide/perindopril 2/0.625mg	2111[&]	30.15	3.67	29.76	2.03/ 0.617mg^	—
Indapamide/perindopril 4/1.25mg	21724[&]	30.40	5.00	29.76	4.09/ 1.22mg[!]	0.36
	21[@]	30	0.00	29.76	4.03/ 1.24mg[!]	
Captopril/HCTZ 25/12.5mg	88[@]	33.70	10.10	29.76	28.32/ 11.04mg^	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients

(refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

Table 5.33 (continued): Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2005

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median[#]	PDD*	
Captopril/HCTZ 50/25mg	283[&]	39.01	17.09	29.76	65.54/ 19.07mg^	1.51
	1022[@]	33.69	13.20	29.76	56.61/ 22.08mg^	
Benazepril 5mg	36[&]	30..0	0.00	29.76	5.04mg^	—
Benazepril 10mg	63[&]	28.57	9.22	29.76	9.60mg^	—
Benazepril 20mg	15[&]	30.00	0.00	29.76	20.16mg[!]	—
Benazepril/HCTZ 10/12.5mg	178[&]	28.06	5.05	29.76	9.43/ 13.26mg^	—
Enalapril/HCTZ 20/12.5mg	1571[&]	30.32	14.35	29.76	20.37/ 12.27mg[?]	0.36
	5031[@]	29.93	4.23	29.76	20.12/ 12.43mg[?]	
Perindopril 4mg	5778[&]	30.37	9.80	29.76	4.08mg[?]	0.09
	20577[@]	30.47	7.57	29.76	4.10mg[?]	
Perindopril 10mg	0.00	0.00	0.00	0.00	0.00	—
Lisinopril/HCTZ 10/12.5mg	1001[&]	30.40	6.19	29.76	10.22mg[?]	1.4
	155[@]	30.77	4.77	29.76	10.34mg[?]	
Lisinopril/HCTZ 20/12.5mg	1648[&]	31.08	8.36	29.76	20.89mg[?]	1.17
	337[@]	30.34	3.41	29.76	20.39mg[?]	
Cilazapril 2.5mg	154[&]	32.10	8.67	29.76	2.70mg[?]	—
Cilazapril 5mg	149[&]	28.98	1.00	29.76	4.87mg[?]	—
Cilazapril/HCTZ 5/12.5mg	287[&]	29.15	5.25	29.76	4.90/ 12.76mg[!]	—
Trandolapril 0.5mg	65[&]	30.22	4.24	29.76	0.51mg^	—
Trandolapril 2mg	514[&]	32.81	8.87	29.76	2.21mg[$]	—
Fosinopril 10mg	301[&]	30.90	5.12	29.76	10.38mg^	—
Fosinopril 20mg	177[&]	31.27	6.87	29.76	21.02mg[!]	—
Fosinopril/HCTZ 20/12.5mg	210[&]	30.36	5.77	29.76	20.40/ 12.25mg[!]	—
Moexipril 7.5mg	508[&]	30.83	4.92	29.76	7.77mg[?]	—
Moexipril 15mg	366[&]	30.89	5.49	29.76	15.57mg[?]	—
Verapamil/Trandolapril 180/2mg	2487[&]	30.56	4.47	29.76	175.26/ 2.05mg[!]	—
Ramipril/Felodipine 2.5/2.5mg	1038[&]	31.29	5.38	29.76	2.04mg^	—
Ramipril/Felodipine 5/5mg	2090[&]	30.81	5.66	29.76	5.18mg[!]	—
Enalapril 2.5mg	82[&]	35.11	13.16	29.76	2.95mg^	0.82
	47[@]	33.83	10.12	29.76	2.84mg^	
Lisinopril/HCTZ 20/25mg	3[@]	30	0.00	29.76	20.16mg[?]	—
Enalapril 5mg	33[@]	29.88	0.48	29.76	5.02mg^	—
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00	0.00	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

As shown in table 5.33 the lowest difference in PPD for the innovators and generics was for lisinopril 5mg with 0.01mg/day and the highest difference was for captopril/HCTZ 50/25mg of 8.93mg/day for 2005. Captopril containing active ingredients also showed the highest difference in 2004.

Table 5.33 reveals that the active ingredient for this period with the highest effect size was ramipril 1.25mg with 1.75 and of practical significance (refer to chapter 4, section 4.8.2.5). The lowest effect size was achieved for perindopril 4mg with 0.09 and therefore of no practical significance. Furthermore, of all the effect sizes 36.84% (n=7 active ingredients) had effect sizes of practical significance between innovator and generic items. This was higher than the previous period. With regard to the previous period three more active ingredients had effect sizes (d-values) in 2005, but four more items had effect sizes of practical significance. Four new active ingredients that showed effect sizes in 2005 with regard to the previous period were indapamide/perindopril 4/1.25mg, ramipril 2.5mg, lisinopril/HCTZ 10/12.5mg and lisinopril/HCTZ 20/12.5mg. This was due to the introduction of generic items.

The following are applicable to table 5.33.

[?] The prescribed daily dose (PDD) of the active ingredient and strength falls within the minimum and maximum maintenance dose range according to the MIMS®. Only nineteen (28.79%) active ACE inhibitor ingredients and strengths fall within this range.

[!] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% of the minimum and maximum maintenance dose range according to the MIMS®. Only ten (15.15%) active ACE inhibitor ingredients and strengths fall within this range.

[$] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% -10% of the minimum and maximum maintenance dose range according to the MIMS®. Only four (6.06%) active ACE inhibitor ingredients and strengths fall within this range.

[^] The prescribed daily dose (PDD) of the active ingredient and strength falls outside 10% of the minimum and maximum maintenance dose range according to the MIMS® and the remaining twenty thirty (50.00%) active ACE inhibitor ingredients and strengths fall within this range.

Many of the active ingredient dosages falling outside the dosage range of the MIMS® might be because some of these dosages were used as initial and not as maintenance dosages.

Table 5.34: Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2006

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Quinapril 5mg	35[&]	28.54	5.29	30.18	4.73mg^	—
Quinapril 10mg	136[&]	29.94	20.09	30.18	9.92mg^	0.49
	20[@]	29.30	0.98	30.18	9.71mg^	
Quinapril 20mg	143[&]	37.91	15.64	30.18	24.62mg[?]	0.82
	48[@]	33.04	9.34	30.18	21.90mg[?]	
Quinapril 40mg	14[&]	28.57	0.94	30.18	37.87mg[?]	—
Quinapril/HCTZ 10/12.5mg	608[&]	30.15	8.71	30.18	9.99mg[!]	1.60
	139[@]	29.42	2.25	30.18	9.75mg[!]	
Quinapril/HCTZ 20/12.5mg	777[&]	30.27	7.99	30.18	20.06mg[!]	1.76
	241[@]	30.02	1.99	30.18	19.90mg[?]	
Captopril 12.5mg	6[&]	35.17	29.26	30.18	14.57mg^	0.05
	21[@]	42.14	17.51	30.18	17.45mg^	
Captopril 25mg	18[&]	80.28	55.69	30.18	33.25mg[∂?]	1.11
	208[@]	44.18	24.72	30.18	18.30mg[∂]	
Captopril 50mg	141[@]	58.24	17.79	30.18	48.24mg[∂?]	—
Enalapril 5mg	134[&]	33.85	14.24	30.18	5.61mg^	0.45
	426[@]	31.90	10.96	30.18	5.29mg^	
Enalapril 10mg	230[&]	36.36	15.10	30.18	12.05mg^	0.45
	1238[@]	31.89	8.95	30.18	10.57mg^	
Enalapril 20mg	301[&]	31.31	11.12	30.18	20.75mg[!]	0.45
	1148[@]	31.06	7.99	30.18	20.58mg[!]	
Lisinopril 2.5mg	0.00	0.00	0.00	30.18	0.00	—
Lisinopril 5mg	36[&]	35.00	16.82	30.18	5.80mg^	0.66
	118[@]	31.14	7.11	30.18	5.16mg^	
Lisinopril 10mg	41[&]	30.00	0.00	30.18	9.94mg^	0.55
	372[@]	32.09	9.63	30.18	10.63mg^	
Lisinopril 20mg	35[&]	34.63	13.81	30.18	22.95mg[?]	0.39
	381[@]	32.22	10.39	30.18	21.35mg[?]	
Ramipril 1.25mg	28[@]	34.29	10.69	30.18	1.42mg^	—
Ramipril 2.5mg	298[&]	32.32	11.11	30.18	2.68mg^	1.17
	646[@]	32.58	8.77	30.18	2.70mg^	
Ramipril 5mg	405[&]	33.84	14.07	30.18	5.61mg[?]	0.28
	940[@]	37.77	19.27	30.18	6.26mg[?]	
Ramipril 10mg	334[&]	31.44	12.44	30.18	10.42mg[!]	0.13
	123[@]	40.00	14.20	30.18	13.25mg^	
Indapamide/perindopril 2/0.625mg	1804[@]	30.23	3.53	30.18	2.00mg 0.624mg^	—
Indapamide/perindopril 4/1.25mg	18347[&]	30.59	5.51	30.18	4.05/ 1.23mg[!]	0.38
	106[@]	30	0.00	30.18	3.98/ 1.26mg[!]	

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

Table 5.34 (continued): Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2006

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Captopril/HCTZ 25/12.5mg	24[@]	30.00	0.00	30.18	24.85/ 12.58mg^	—
Captopril/HCTZ 50/25mg	177[&]	43.47	22.79	30.18	72.03/ 17.35mg[?]	1.34
	405[@]	31.60	12.45	30.18	52.36/ 23.87mg[?]	
Benazepril 5mg	19[&]	33.16	9.46	30.18	5.49mg^	—
Benazepril 10mg	26[&]	30.27	6.02	30.18	10.03mg^	—
Benazepril 20mg	0.00	0.00	0.00	0.00	0.00	—
Benazepril/HCTZ 10/12.5mg	160[&]	29.01	4.59	30.18	9.61/ 13.01mg[!]	—
Enalapril/HCTZ 20/12.5mg	384[&]	32.34	28.18	30.18	21.43/ 11.67mg[?]	0.25
	1350[@]	31.08	7.13	30.18	20.60/ 12.14mg[?]	
Perindopril 4mg	3014[&]	30.68	8.83	30.18	4.07mg[?]	0.13
	14327[@]	30.52	7.52	30.18	4.04mg[?]	
Perindopril 10mg	229[&]	30.76	10.11	30.18	10.19mg[!]	—
Lisinopril/HCTZ 10/12.5mg	159[&]	33.58	11.25	30.18	11.13mg[?]	0.25
	483[@]	31.49	7.07	30.18	10.43mg[?]	
Lisinopril/HCTZ 20/12.5mg	259[&]	33.59	14.38	30.18	22.26mg[?]	0.37
	617[@]	30.63	4.31	30.18	20.30mg[?]	
Cilazapril 2.5mg	30[&]	37.87	13.07	30.18	3.14mg[?]	—
Cilazapril 5mg	14[&]	28.14	0.53	30.18	4.66mg[?]	—
Cilazapril/HCTZ 5/12.5mg	48[&]	25.33	6.30	30.18	4.20/ 14.89mg^	—
Trandolapril 0.5mg	1[&]	20.00	0.00	30.18	0.33mg^	—
Trandolapril 2mg	233[&]	33.22	9.71	30.18	2.20mg[$]	—
Fosinopril 10mg	52[&]	30.06	5.14	30.18	9.96mg^	1.01
	19[@]	30.00	0.00	30.18	9.94mg^	
Fosinopril 20mg	12[&]	37.50	13.57	30.18	24.85mg[?]	0.24
	6[@]	30.00	0.00	30.18	19.88mg[!]	
Fosinopril/HCTZ 20/12.5mg	30[&]	30.00	0.00	30.18	19.88/ 12.58mg[!]	—
Moexipril 7.5mg	340[&]	30.18	2.30	30.18	7.50mg[?]	—
Moexipril 15mg	361[&]	30.80	5.00	30.18	15.31mg[?]	—
Verapamil/Trandolapril 180/2mg	1505[&]	30.58	5.27	30.18	177.66/ 2.03mg[!]	—
Ramipril/Felodipine 2.5/2.5mg	518[&]	31.10	8.38	30.18	2.58mg[!]	—
Ramipril/Felodipine 5/5mg	1030[&]	31.21	8.18	30.18	5.17mg[!]	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients (refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

Table 5.34 (continued): Summary of the prescribed daily dose and effect size of ACE inhibitor innovators and generics for 2006

Active ingredient	Frequency (N)	Quantity tabs. or caps. per prescription				Effect size (d-value)**
		Mean	Standard deviation (±)	Median#	PDD*	
Enalapril 2.5mg	12[&]	51.50	10.52	30.18	4.27mg^	2.19
	2[@]	30.00	0.00	30.18	2.49mg^	
Lisinopril/HCTZ 20/25mg	14[@]	30.00	0.00	30.18	19.88mg[?]	—
Enalapril 5mg	1[@]	30.00	0.00	30.18	4.97^	—
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00	0.00	—

∂ Twice daily dosage

* Prescribed daily dose (refer to chapter 3, section 3.2.8.2)

** Effect size (refer to chapter 4, section 4.8.2.5)

The average median was determined by adding all the medians of all the active ingredients and dividing it by the number of active ingredients. (refer to chapter 4, section 4.8.2.6).

[&] (Innovator) / [@] (Generic).

As shown in table 5.34 the largest difference in PDD between the innovator and generic item was for captopril/HCTZ 50/25mg of 19.76mg/day and the smallest difference was for fosinopril 10mg and ramipril 2.5mg of 0.02mg/day. Captopril/HCTZ also showed the highest difference in PDD between innovator and generic in the previous period, and therefore the difference in the prescribed daily dose between innovator and generic was the largest for this active ingredient.

In table 5.34 the active ingredient for this period with the highest effect size was enalapril 2.5mg with 2.19 and of practical significance (refer to chapter 4, section 4.8.2.5). The lowest effect size was for captopril 12.5mg with 0.05 and therefore of no practical significance. Captopril 12.5mg had the largest difference in 2004. Furthermore, of all the effect sizes 33.33% (n=8 active ingredients) had effect sizes of practical significance between innovator and generic items. This was lower than the previous period. With regard to the previous period five more active ingredients had effect sizes (d-values) in 2005, but one more item had an effect size of practical significance. Six new active ingredients that showed effect sizes in 2005 with regard to the previous period were quinapril 10mg, quinapril 20mg, quinapril/HCTZ 10/12.5mg, quinapril/HCTZ 20/12.5mg, fosinopril 10mg and fosinopril 20mg. This was due to the introduction of generic items. During 2006 there were two active ingredients that had effect sizes in 2005 but not in 2006, namely captopril 50mg and ramipril 1.25mg.

The following are applicable to table 5.34.

[?] The prescribed daily dose (PDD) of the active ingredient and strength falls within the minimum and maximum maintenance dose range according to the MIMS®. Only twenty three (31.94%) active ACE inhibitor ingredients and strengths fall within this range.

[!] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% of the minimum and maximum maintenance dose range according to the MIMS®. Only seventeen (23.61%) active ACE inhibitor ingredients and strengths fall within this range.

[$] The prescribed daily dose (PDD) of the active ingredient and strength falls within 5% -10% of the minimum and maximum maintenance dose range according to the MIMS®. Only one (1.34%) active ACE inhibitor ingredients and strengths fall within this range.

[^] The prescribed daily dose (PDD) of the active ingredient and strength falls outside 10% of the minimum and maximum maintenance dose range according to the MIMS® and the remaining thirty one (43.06%) active ACE inhibitor ingredients and strengths fall within this range.

The reasons for many of the active ingredient dosages falling outside the dosage range of the MIMS® might be because some of these dosages were used as initial and not as maintenance dosages.

Table 5.35: Average cost per ACE inhibitor active ingredient innovators and generics for 2005 and 2006

Active ingredient	2005		2006	
	Average cost /item (R)	standard deviation (±)	Average cost /item (R)	standard deviation (±)
Quinapril 5mg	88.60[&]	46.93	37.81[&]	50.00
Quinapril 10mg	145.54[&]	52.55	127.42[&]	86.51
	0.00	0.00	84.79[@]	6.82
Quinapril 20mg	236.75[&]	100.68	248.36[&]	125.07
	0.00	0.00	146.20[@]	42.63
Quinapril 40mg	183.77[&]	39.56	214.88[&]	36.47
Quinapril/HCTZ 10/12.5mg	143.78[&]	25.87	149.26[&]	39.36
	0.00	0.00	86.14[@]	6.08
Quinapril/HCTZ 20/12.5mg	215.17[&]	34.95	224.80[&]	52.87
	0.00	0.00	131.65[@]	8.51
Captopril 12.5mg	33.91[&]	36.28	31.31[&]	30.51
	19.92[@]	11.53	29.72[@]	9.90
Captopril 25mg	124.20[&]	131.09	193.06[&]	155.73
	24.31[@]	18.64	20.50[@]	14.19
Captopril 50mg	145.34[&]	89.20	0.00	0.00
	42.94[@]	17.83	46.23[@]	15.21
Enalapril 5mg	36.15[&]	15.38	39.73[&]	15.26
	30.57[@]	13.48	32.93[@]	11.53
Enalapril 10mg	53.69[&]	23.60	59.72[&]	28.05
	43.04[@]	14.28	47.04[@]	12.49
Enalapril 20mg	86.66[&]	30.28	93.77[&]	30.95
	71.85	19.40	79.74[@]	20.63
Lisinopril 2.5mg	0.00	0.00	0.00	0.00
Lisinopril 5mg	52.73[&]	35.67	54.54[&]	21.20
	34.47[@]	8.59	40.66[@]	10.41
Lisinopril 10mg	74.77[&]	37.99	67.27[&]	7.89
	49.56[@]	8.42	60.20[@]	12.97
Lisinopril 20mg	103.81[&]	77.47	108.48[&]	49.40
	76.26[@]	22.21	89.05[@]	25.13
Ramipril 1.25mg	140.30[&]	38.77	0.00	0.00
	72.49[@]	18.85	80.18[@]	25.06
Ramipril 2.5mg	167.98[&]	53.68	172.25[&]	62.04
	95.46[@]	26.24	99.59[@]	26.29
Ramipril 5mg	230.93[&]	125.58	225.16[&]	139.42
	177.72[@]	80.69	186.09[@]	96.65
Ramipril 10mg	260.07[&]	101.02	229.86[&]	105.77
	0.00	0.00	216.26[@]	71.41
Indapamide/perindopril 2/0.625mg	201.90[&]	30.98	214.44[&]	22.41
	0.00	0.00	0.00	0.00
Indapamide/perindopril 4/1.25mg	211.17[&]	39.18	201.06[&]	40.87
	225.29[@]	10.17	216.79[@]	20.65
Captopril/HCTZ 25/12.5mg	50.66[@]	15.08	53.57[@]	2.33
Captopril/HCTZ 50/25mg	241.26[&]	111.43	273.15[&]	141.98
	73.19[@]	23.22	82.99[@]	23.03

[&] (Innovator) / [@] (Generic).

Table 5.35 (continued): Average cost per ACE inhibitor active ingredient innovators and generics for 2005 and 2006

Active ingredient	2005		2006	
	Average cost /item (R)	standard deviation (±)	Average cost /item (R)	standard deviation (±)
Benazepril 5mg	132.90[&]	11.58	156.13[&]	43.94
Benazepril 10mg	149.58[&]	51.56	170.25[&]	32.44
Benazepril 20mg	251.40[&]	23.08	0.00	0.00
Benazepril/HCTZ 10/12.5mg	272.67[&]	53.42	286.17[&]	42.40
Enalapril/HCTZ 20/12.5mg	95.34[&]	45.86	112.83[&]	82.21
	79.03	12.46	92.03[@]	22.08
Perindopril 4mg	140.24[&]	41.95	150.92[&]	37.94
	144.02	37.74	155.75[@]	36.82
Perindopril 10mg	0.00	0.00	281.65[@]	94.30
Lisinopril/HCTZ 10/12.5mg	116.05[&]	33.18	75.36[&]	20.78
	69.45	17.34	70.10[@]	16.22
Lisinopril/HCTZ 20/12.5mg	190.13[&]	68.99	131.33[&]	44.75
	109.03	23.46	114.66[@]	18.33
Cilazapril 2.5mg	156.02[&]	48.71	207.24[@]	76.38
Cilazapril 5mg	148.79[&]	9.31	171.19[@]	2.34
Cilazapril/HCTZ 5/12.5mg	152.89	22.27	154.51[@]	31.57
Trandolapril 0.5mg	130.07[&]	19.27	84.75[&]	0.00
Trandolapril 2mg	147.80[&]	41.40	159.52[&]	40.77
Fosinopril 10mg	175.62[&]	27.52	165.41[&]	35.90
	0.00	0.00	129.02[@]	4.77
Fosinopril 20mg	206.09[&]	40.66	205.97[&]	121.12
			177.09[@]	0.00
Fosinopril/HCTZ 20/12.5mg	230.78[&]	40.19	248.12[&]	33.45
Moexipril 7.5mg	116.64[&]	18.42	114.03[&]	8.51
Moexipril 15mg	199.37[&]	30.30	199.39[&]	29.22
Verapamil/Trandolapril 180/2mg	284.86[&]	45.30	306.88[&]	40.81
Ramipril/Felodipine 2.5/2.5mg	187.99[&]	35.65	210.36[&]	41.91
Ramipril/Felodipine 5/5mg	281.70[&]	57.85	320.75[&]	68.44
Enalapril 2.5mg	56.67[&]	19.41	92.14[&]	21.60
	40.72	11.94	44.94[@]	0.00
Lisinopril/HCTZ 20/25mg	128.86	23.66	124.73[@]	0.92
Enalapril 5mg	19.20	0.90	17.85[@]	0.00
Ramipril/HCTZ 2.5/5mg	0.00	0.00	0.00	0.00

[&] (Innovator) / [@] (Generic).

5.10 Interpharm® top 50 versus Mediscor® top 50 with reference to ACE inhibitors

5.10.1 Introduction

In this section the ACE inhibitors that were prevalent in the top 50 medicine items claimed through Interpharm® Datasystems for the year 2002, 2004 and 2005 are compared to the ACE inhibitors that were prevalent in the top 50 list of Mediscor® for the same time periods. These items are listed according to their contribution to the total expenditure of all items from Mediscor® and Interpharm® Datasystems. Both Interpharm® Datasystems whose data were used in this study and Mediscor® are medical scheme administrators.

- *Year 2002*

Table 5.36: Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2002

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
1	Lipitor® 10mg tabs.		1	Lipitor® 10mg tabs.
2	Lipitor® 20mg tabs.		2	Cipramil® 20mg tabs.
3	Cipramil® 20mg tabs.		3	Lipitor® 20mg tabs.
4	Vioxx® 25mg tabs.		4	Aropax® 20mg tabs.
5	Celebrex® 200mg caps.		5	Combivir® tabs.
6	Aropax® 20mg tabs.		6	Myprodol® caps.
7	Lanzor® 30mg caps.		7	Vioxx® 25mg tabs.
8	Premarin® 0.625mg tabs.		8	Lanzor® 30mg caps.
9	**Coversyl® 4mg tabs.**		9	Flixonase® AQ Spray.
10	Livifem® 2.5mg tabs.		10	Actraphane® Penset 3ml.
11	Fosamax® 10mg tabs.		**11**	**Coversyl® 4mg tabs.**
12	Norvasc® 5mg tabs.		12	Stocrin® 200mg caps.
13	Myprodol® caps.		13	Zyrtec® 10mg tabs.
14	Losec® MUPS 20mg tabs.		14	Zoloft® 50mg tabs.
15	Flixonase® AQ Spray		15	Zinnat® 250mg tabs.
16	Seretide® Accuhaler 50/250		16	Norvasc® 5mg tabs.
17	Stilnox® 10mg tabs.		17	Stilnox® 10mg tabs.
18	Roaccutane® 20mg caps.		18	Losec® MUPS 20mg tabs.
19	Premarin® 1.25mg tabs.		19	Celebrex® 200mg caps.
20	Zyrtec® 10mg tabs.		20	Premarin® 0.625mg tabs.
21	Co-Diovan® 80/12.5mg tabs.		21	Seretide® 50/250 inhaler
22	Cozaar Comp.® tabs.		22	Orelox Junior® suspension
23	Zocor® 20mg tabs.		23	Synap Forte® tabs.
24	Zinnat® 250mg tabs.		24	Sporanox® 100mg caps.
25	Lanzor® 15mg caps.		25	Augmentin® BD 1000mg. tabs.
26	Eltroxin® 100mcg tabs.		26	Cataflam® dispersable tabs.
27	Zoloft® 50mg tabs.		**27**	**Coversyl Plus® tabs.**
28	Clarityne® 10mg tabs.		28	Mybulen® tabs.
29	Mobic® 7.5mg tabs.		29	Mobic® 7.5mg tabs.

*Adapted from Bester *et al.* (2003).

Table 5.36 (continued): Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2002

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
30	Synap Forte® tabs.		30	Nasonex® 140 metered spray
31	Cozaar® 50mg tabs.		31	Orelox® 100mg tabs.
32	**Zestoretic® 20/12.5mg tabs.**		32	Videx® 100mg tabs.
33	Zocor® 10mg tabs.		33	Nuzak® 20mg caps.
34	Norvasc® 10mg tabs.		34	Zocor® 20mg caps.
35	**Coversyl Plus® tabs.**		35	Norvasc® 10mg tabs.
36	Estrofem® 2mg tabs.		36	Zocor® 10mg caps.
37	Actraphane® HM Penset 3ml.		37	Co-Diovan® 80mg tabs.
38	Diovan® 80mg caps.		38	Celestamine® tabs.
39	Evista® 60mg tabs.		39	Livifem® tabs.
40	Efexor XR® 150mg caps.		40	Roaccutane® 10mg caps.
41	Augmentin® 1000mg BD tabs.		41	Cozaar Comp.® tabs.
42	Fosamax® 70mg tabs.		42	Lanzor® 15mg. caps.
43	Adalat XL® 30mg tabs.		43	Zithromax® 500mg tabs.
44	Kliogest® tabs.		44	Lentogesic® caps.
45	Imovane® 7.5mg tabs.		45	Humalog® Mix 25 penset
46	**Accuretic® 20/12.5mg tabs.**		46	Adalat XL® 30mg tabs.
47	Mybulen® tabs.		47	Eltroxin® 0.1mg tabs.
48	Pantoloc® 40mg tabs.		48	Cozaar® 50mg tabs.
49	Natralix SR® 1.5mg tabs.		49	Telfast® 120mg tabs.
50	Combivir® tabs.		50	Zinnat® 125mg/5ml suspension

*Adapted from Bester *et al.* (2003).

According to table 5.36, the top 50 items according to total expenditure claimed through Mediscor® included four ACE inhibitors of which three are combination items and one a single agent. Interpharm® however only had two ACE inhibitors under the top 50 items. The item with the highest expenditure of the ACE inhibitors by Mediscor® was Coversyl® 4mg in position 9 as well as Interpharm® in position 11. Zestoretic® 20/12.5mg was claimed by Mediscor® in position 32, but this item was not claimed under the top 50 by Interpharm®.

The third ACE inhibitor claimed by Mediscor® was the combination item, Coversyl Plus® which came in at position 35. This item was in position 27 with regard to Interpharm®.

It can be concluded that more ACE inhibitor items were claimed by Mediscor® than by Interpharm® during this period.

- *Year 2004*

Table 5.37: Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2004

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
1	Lipitor® 10mg tabs.		1	Lipitor® 10mg tabs.
2	Lipitor® 20mg tabs.		2	Combivir® tabs.
3	Vioxx® 25mg tabs		3	Stocrin® 200mg caps.
4	Fosamax® 70mg tabs.		4	Lipitor® 20mg tabs.
5	Celebrex® 200mg caps.		5	Vioxx® 25mg tabs.
6	Aropax® 20mg tabs.		6	Myprodol® caps.
7	Cilift® 20mg tabs.		7	Aropax® 20mg tabs.
8	Premarin® 0.625mg tabs.		**8**	**Coversyl Plus® tabs.**
9	Norvasc® 5mg tabs.		9	Viramune® 200mg tabs.
10	**Coversyl Plus® tabs.**		10	Celebrex® 200mg caps.
11	Myprodol® caps.		11	Actraphane® Penset 3ml.
12	Lanzor® 30mg caps.		12	Seretide® 50/250 inhaler
13	Livifem® 2.5mg tabs.		13	Cataflam Disp. 50mg tabs.
14	Adco-Simvastatin® 20mg tabs.		14	Lanzor® 30mg caps.
15	Seretide® Accuhaler 50/250		15	Cilift® 20mg tabs.
16	Nexiam® 40mg tabs.		16	Norvasc® 5mg tabs.
17	Eltroxin® 100mcg tabs.		17	Fosamax® 1 weekly tbas.
18	Flixonase® AQ. spray		18	Flixonase® AQ. spray
19	Synap Forte® tabs.		19	Nexiam® 40mg tabs.
20	Augmentin® BD 1000mg tabs.		20	Adco-Simvastatin® 20mg tabs.
21	Klacid® XL 500mg tas.		21	Sporanox® 100mg caps.
22	Cozaar Comp.® tabs		22	Premarin® 0.625mg tabs.
23	Co-Diovan® 80/12.5mg		23	Augmentin® BD 1000mg tabs.
24	Efexor XR® 150mg caps.		24	Norvasc® 10mg tabs.
25	Nexiam® 20mg tabs.		25	Co-Diovan® 80mg tabs.
26	Premarin® 1.25mg tabs.		**26**	**Prexum® 4mg tabs.**
27	Actraphane® HM penset		27	Losec® MUPS 20mg tabs.
28	Lanzor® 15mg caps.		28	Eltroxin® 100mcg tabs.
29	Losec® 20mg MUPS		29	Adalat XL® 30mg tabs.
30	Norvasc® 10mg tabs.		30	Humalog® Mix 25 Penset
31	Concor® 5mg tabs.		31	Orelox® Junior suspension
1364 to 32	**Prexum® 4mg tabs.**		32	Mybulen® tabs.
33	Zoloft® 50mg tabs.		33	Zoloft® 50mg tabs.
34	Efexor XR® 75mg caps.		34	Synap Forte® tabs.
35	Adalat XL® 30mg tabs.		35	Co-Diovan® 160mg tabs.
36	Cipramil® 20mg tabs.		36	Klacid® XL 500mg tabs.
37	Avelon® 400mg tabs.		37	Cozaar Comp.® tabs.
38	Sporanox® 100mg caps.		38	Efexor XR® 75mg caps.
39	Estrofem® 2mg tabs.		39	Eprex® 4000 Prefill
40	Mybulen® tabs.		40	Nasonex® 140 Metered spray
41	Plavix® 75mg filmcoated tabs.		41	Nexiam® 20mg tabs.
42	**Coversyl® 4mg tabs.**		**42**	**Coversyl® 4mg tabs.**
43	Cozaar® 50mg. tabs		43	Avelon® 400mg tabs.
44	Adco-Simvastatin® 40mg tabs.		44	Concor® 5mg tabs.
45	Pantoloc® 40mg tabs.		45	Orelox® 100mg tabs.

*Adapted from Bester and Hammann (2005).

Table 5.37(continued): Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2004

Mediscor®*		Interpharm®	
Ranked	Product name	Ranked	Product name
46	Adco-Zolpidem® 10mg tabs.	46	Livifem® tabs.
47	Adco-Simvastatin® 10mg tabs.	47	Cipramil® 20mg tabs.
48	Atacand Plus® tabs.	48	Diovan® 80mg tabs.
49	Atacand® 16mg tabs.	49	Lescol® XL 80mg tabs.
50	Cataflam® Disp. 50mg tabs.	50	Lanzor® 15mg caps.

*Adapted from Bester and Hammann (2005).

As shown in table 5.37, and according to total expenditure, only three ACE inhibitors (Coversyl Plus®, Coversyl® and Prexum®) were claimed by Mediscor® as well as by Interpharm®, and interestingly is that the same items claimed by Mediscor® were also claimed by Interpharm®. The item that contributed the most to the total expenditure of both these two databases was the combination item, Coversyl Plus® in position 10 (Mediscor®) and position 8 (Interpharm®). This item moved up in the ranks from position 35 and 27 respectively.

The fact that combination items moved up in the ranks might be attributed to the fact that that prescribers realise the benefits of using combination therapy in the treatment of hypertension (refer to chapter 2, section 2.3.3).

Furthermore, Coversyl® moved down to position 42 in both databases, but this item still remained under the top 50 items for both databases.

This period also showed the introduction of the Coversyl® generic, namely Prexum® into the top 50 list of both databases. Prexum® was in position 32 (Mediscor®) and position 26 (Interpharm®) which are both much higher than the innovator item. In addition to this Prexum® moved up from position 1364 in 2003 to 32. The fact that Prexum® is at such high positions might be attributed to the fact that prescribers and dispensers realise the potential benefits of using generic substitution (refer to chapter 2, section 2.4).

Bester *et al.* (2005) contributed by stating that Prexum® which is one of eight antihypertensive products in the top 50 list, continues to move up in the ranks, replacing its originator Coversyl®. Coversyl Plus® is however following closely.

- *Year 2005*

Table 5.38: Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2005

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
1	Lipitor® 10mg tabs.		1	Combivir® tabs.
2	Lipitor® 20mg tabs.		2	Stocrin® 600mg tabs.
3	Fosamax® 70mg tabs.		3	Lipitor® 10mg tabs.
4	Celebrex® 200mg caps.		**4**	**Coversyl Plus® tabs.**
5	Adco-Simvastatin® 20mg tabs.		5	Viramune® tabs.
6	**Prexum® 4mg tabs.**		6	Myprodol® caps.
7	**Coversyl Plus® tabs.**		7	Lipitor® 20mg tabs.
8	Cipralex® 10mg tabs.		8	Stocrin® 200mg caps.
9	Nexiam® 40mg tabs.		**9**	**Prexum® 4mg tabs.**
10	Myprodol® caps.		10	Cataflam Disp.® 50mg. tabs.
11	Premarin® 0.625mg tabs.		11	Celebrex® 200mg caps.
12	Aropax® 20mg tabs.		12	Aspen-Lamzid®
13	Seretide Accuhaler® 50/250		13	Lanzor® 30mg caps.
14	Eltroxin® 100mcg tabs.		14	Seretide® 50/250 inhaler
15	Klacid® XL 500mg tabs.		15	Aropax® 20mg
16	Synap Forte® tabs.		16	Mybulen® tabs.
17	Cilift® 20mg. Tabs.		17	Lamisil®
18	Avelon® 400mg tabs.		18	Adco-Amoclav® BD 1000mg
19	Livifem® 2.5mg tabs.		19	Deselex®
20	Plavix® 75mg filmcoated tabs.		20	Co-Diovan® 160/12.5mg tabs.
21	Nexiam® 20mg		21	Nexiam® 40mg
22	Flixonase AQ® Nasal Spray		22	Sporanox® 100mg caps.
23	Stocrin® 600mg		23	Efexor XR® 75mg caps.
24	Lanzor® 30mg caps.		24	Adalat® XL 30mg tabs.
25	Sporanox® 100mg caps.		25	Co-Diovan® 80/12.5mg
26	Cozaar Comp® tabs.		26	Pariet® 20mg
27	Adalat XL® 30mg tabs.		27	3TC® 150mg tabs.
28	Tavanic® 500mg		28	Fosamax® 1 weekly tabs.
29	Actraphane HM® Penset		29	Avelon® 400mg
30	Gleevec® 100mg caps.		30	Premarin® 0.625mg tabs.
31	Adco-Amoclav® BD 1000mg		31	Adco-Simvastatin® 20mg tabs.
32	Co-Diovan® 80/12.5mg		32	Orelox® Junior suspension
33	Efexor XR® 150mg caps.		33	Klacid® XL 500mg tabs.
34	Efexor XR® 75mg caps.		34	Flixonase® Aqueous 120 dose
35	Novomix 30® Flexpen		35	Xyzal® 5mg
36	Aspen Lamzid® tabs.		36	Actraphane® Penset 3ml.
37	Adco-Simvastatin® 10mg		37	Cipralex® 10mg
38	Norvasc® 5mg tabs.		38	Synap Forte® tabs.
39	Pantoloc® 40mg tabs.		39	Eltroxin® 100mcg tabs.
40	Lipitor® 40mg tabs.		40	Norvasc® 5mg tabs.

*Adapted from Bester *et al.* (2006).

Table 5.38(continued): Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2005

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
41	Cataflam Disp®. 50mg. tabs.		41	Zithromax® 500mg tabs.
42	Adco-Simvaststin® 40mg tabs.		42	Adalat XL® 60mg tabs.
43	Atacand Plus® 6/12mg tabs.		43	Tavanic® 500mg tabs.
44	Mybulen® tabs.		44	Zelnorm® 6mg tabs.
45	Ketek® 400mg tabs.		45	Norvasc® 10mg tabs.
46	Coxflam® 15mg		46	Efexor XR® 15mg caps.
47	Zithromax® 500mg tabs.		47	Zelitrex® 500mg tabs.
48	Cozaar® 50mg tabs.		48	Ceroxim® 500mg tabs.
49	Estrofem® 2mg tabs.		49	Controloc® 40mg tabs.
50	Co-Diovan® 160/12.5mg tabs.		50	Lescol® XL 80mg tabs.

*Adapted from Bester *et al.* (2006).

Table 5.38 reveals that for the first time only two ACE inhibitors were claimed (Coversyl Plus® and Prexum®) (according to total expenditure) at Mediscor® as well as Interpharm®. Again the same ACE inhibitors appeared under the top 50 except for Coversyl®, which did not appear in the top 50 of either Mediscor® or Interpharm®. With regard to Mediscor®, both Prexum® and Coversyl Plus® were at their highest positions on the top 50 list during 2006. Prexum® moved up 26 positions to position number 6 and Coversyl Plus® moved up 35 positions to number seven on the list. With regard to Interpharm®, Coversyl Plus® moved up 4 positions to number 4 and Prexum® moved up 17 positions to number 9. Coversyl Plus®, therefore had a higher position at Interpharm®, but Prexum® had a higher position on Mediscor®.

It can therefore be concluded that for both databases, both of these items (Coversyl® and Prexum®), were under the top 10 for the first time. This approach also underlines the importance of a selected database.

- *Year 2006*

Table 5.39: Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2006

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
1	Lipitor® 10mg tabs.		1	Combivir® tabs.
2	Lipitor® 20mg tabs.		2	Stocrin® 600mg tabs.
3	Cipralex® 10mg tabs.		3	Aspen Lamzid® tabs.
4	Fosamax® 70mg tabs.		4	Viramune® tabs.
5	Celebrex® 200mg caps.		5	Lipitor® 10mg tabs.
6	**Prexum® 4mg tabs.**		6	Lipitor® 20mg tabs.
7	Nexiam® 40mg tabs.		**7**	**Prexum® tabs.**
8	Adco-Simvastatin® 20mg tabs.		8	Celebrex® 200mg caps.
9	Synap Forte® tabs.		**9**	**Coversyl Plus® tabs.**
10	Eltroxin® 100mcg tabs.		10	Sporanox®
11	Avelon® 400mg tabs.		11	Co-Diovan® 160/12.5mg tabs.
12	Premarin® 0.625mg tabs.		12	Xyzal® 5mg
13	Klacid XL® 500mg tabs.		13	Seretide® 50/250 Accuhaler
14	Plavix® 75mg tabs.		14	Deselex®
15	Tavanic® 500mg tabs.		**15**	**Prexum Plus® tabs.**
16	Seretide® Accuhaler 50/250		16	Betavit® caps.
17	Herceptin® Inj.		17	Adalat XL® 30mg tabs.
18	Nexiam® 20mg tabs.		18	Adco-Amoclav® BD 1000mg
19	Livifem® 2.5mg tabs.		19	Mybulen® tabs.
20	**Prexum Plus® tabs.**		20	Celestamine® tabs.
21	Stocrin® 600mg tabs.		21	Stocrin® 200mg caps.
22	Gleevec® 400mg tabs.		22	Pariet® 20mg tabs.
23	Aspen Lamzid® tabs.		23	3TC® 150mg tabs.
24	**Coversyl Plus® tabs.**		24	Efexor XR® 75mg caps.
25	Novomix® 30 Flexpen		25	Dicloflam® Blackcurrent
26	Adco-Simvastatin® 40mg tabs.		26	Nexiam® 40mg tabs.
27	Ketek® 400mg tabs.		27	Lacteol Forte®
28	Coxflam® 15mg tabs.		28	Aspen Nevirapine® tabs.
29	Adalat XL® 30mg tabs.		29	Ibupain® Forte
30	Deselex® 5mg tabs.		30	Co-Diovan® 80/12.5mg tabs.
31	Lipitor® 40mg tabs.		31	Avelon® 400mg tabs.
32	Mabthera® 500mg vial		32	Ceroxim® 500mg tabs.
33	Adco-Zolpidem® 10mg tabs.		33	Amloc® 10mg tabs.
34	Cymbalta® 60mg caps.		34	Lescol® XL 80mg caps.
35	Adco-Simvastatin® 10mg tabs.		35	Nasonex Aqueous® 140
36	Sporanox® 100mg caps.		36	Nasacor T® 120 dose
37	Cozaar Comp.® Tabs.		37	Ziagen® 300mg tabs.
38	Co-Diovan® 80/12.5mg tabs.		38	Fosamax® Once Weekly
39	Atacand Plus® 16/12.5mg		39	Plavix® 75mg tabs.
40	Co-Diovan® 160/12.5mg tabs.		40	Kaletra® caps.

*Adapted from Bester and Hammann (2007).

Table 5.39 (continued): Comparison between Mediscor® and Interpharm®'s top 50 products according to total expenditure for 2006

Mediscor®*			Interpharm®	
Ranked	**Product name**		**Ranked**	**Product name**
41	Cilift® 20mg tabs.		41	Zantac® Effervescent 150mg
42	Efexor XR® 150mg caps.		42	Sandoz Co-Amoclav® 1000mg tabs.
43	Myprodol® caps.		43	Tavanic® 500mg tabs.
44	Adco-Amoclav® BD 1000mg tabs.		44	Zinnat® suspension
45	Estrofem® 2mg tabs.		45	Seretide® 50/500 Accuhaler
46	Flomist® AQ Nasal Spray		46	Andolex-C® oral rinse
47	Nasonex® AQ Nasal Spray		47	Adco-Zolpidem® tabs.
48	Lansoloc® 30mg caps.		48	Aspen-Azithromycin® 500mg tabs.
49	Actraphane® Penset		49	Adalat XL® 60mg tabs.
50	Efexor XR® 75mg caps.		50	Zelnorm® 6mg tabs.

*Adapted from Bester and Hammann (2007).

According to table 5.39 Prexum® was at position 6 at Mediscor® according to total expenditure, which is the same position as 2005. Prexum® was at position 7 at Interpharm® which is 2 positions higher than 2005. For the first time Prexum Plus® (generic of Coversyl Plus®) was on the top 50 list of at Mediscor® at position 20. Coversyl Plus® however, moved down 17 positions to number 24. Interpharm® had Coversyl Plus® position 9 after moving down 5 positions. This year also showed the introduction of Prexum Plus® into the top 50 list of Interpharm® at position 15.

It can be concluded from this year that the ACE inhibitor generic items showed increases in expenditure and therefore moved up in the top 50 list of both Mediscor® and Interpharm®. The ACE inhibitor combination items also showed increases in positions on the list, especially with the introduction of generic combination items.

This approach of comparing different databases with each other also underlines the importance of using a selected database for analyses. Whilst the ACE inhibitors follow the same "trends", a difference in usage patterns does exist.

5.11 Chapter summary

This chapter contained the results of the empirical investigation. The prescribing patterns and costs of the ACE inhibitors were are discussed and with regard to the implementation of pricing regulations implemented in 2004. The latter form is considered as an important part of this study.

Chapter 6 will contain the conclusion, recommendations and limitation of this study.

Chapter 6

Conclusions, recommendations and limitations

6.1 Introduction

In this chapter the conclusions based on the results of the literature review and the empirical investigation as well as recommendations derived from this study are discussed. The limitations encountered during the study will also be included in the study.

6.2 Conclusions

6.2.1 Conclusions based on the literature study

The following conclusions are based on the specific objectives of the literature study (refer to chapter 1 to chapter 4).

The ***first specific research objective*** of the study was to review and discuss hypertension and congestive heart failure as diseases as well as the management thereof (refer to chapter 2, section 2.2.1 and 2.2.2). Further it included the use of particularly ACE inhibitors in the management of these diseases (refer to chapter 2, section 2.2.1.14.6, 2.2.1.14.7 and 2.2.2.8.1.1).

The ***second specific research objective*** of the study was to outline the prevalence of hypertension and congestive heart failure because cardiovascular disease is going to be the leading cause of death and disability by 2020 as stated by Gaziano (2005:3569). According to Steyn *et al.* (2001:1720) approximately one-fifth of the South African adult population have hypertension. The overall prevalence rates, age-adjusted to the South African population, for men and women were 20.9% and 21.2% respectively (refer to chapter 2, section 2.2.1.3). From 1990 to 1999, the annual number of hospitalizations in the United States increased from approximately 810 000 to over 1 million for heart failure as a primary diagnosis, and from 2.4 to 3.6 million for heart failure as a primary or secondary diagnosis. In 2001 nearly 53 000 patients died of heart failure as a primary cause in the United States (Hunt *et al.*, 2005:1117-1118) (refer to chapter 2, section 2.2.2.2).

The ***third specific research objective*** of the study was to determine what the "new" pricing regulations implemented in 2004 entailed, which included the definition of the single exit price (SEP) method for setting the SEP and the way in which the SEP was calculated. Furthermore, this research objective included aspects of the Supreme Court appeal and expected savings from the SEP. This research objective concluded with the effects and consequences of the implementation of the "new" pricing regulations (refer to chapter 3, section 3.4).

The ***fourth specific research objective*** of the study was to investigate the relevance of using combination therapy in conjunction with ACE inhibitors for cardiovascular diseases. The literature included aspects on how to use combination therapy, advantages and disadvantages as well as the different types of drug combinations for use in hypertension. This research objective concluded with the benefits of using ACE inhibitors with different antihypertensive products (refer to chapter 2, section 2.3.6.1 to 2.3.6.4).

The ***fifth specific research objective*** of the study was to review the basic aspects of pharmacoeconomics (refer to chapter 3, section 3.1). Terms were defined and discussed as well as the application of pharmacoeconomics to ACE inhibitors. Different methodologies and limitations of pharmacoeconomics were discussed to show the relevance of using these tools as an aid in decision making.

The ***sixth specific research objective*** of the study was to define and discuss the fundamentals of drug utilisation review (refer to chapter 3, section 3.2). In addition to this a classification of drug utilisation review was done and applied to ACE inhibitors. The types of drug utilisation review were also listed and discussed and the limitations of drug utilisation review were also discussed and concluded with the integration between drug utilisation review and pharmacoeconomics (refer to chapter 3, section 3.2.10). This research objective further included the nature, advantages and disadvantages of managed care and concluded with the integration between managed care and pharmacoeconomics (refer to chapter 3, section 3.3.5).

The ***seventh specific research objective*** of the study was to discuss the basic aspects of generic substitution. A conceptual model for generic drug use was also illustrated and discussed (refer to chapter 2, section 2.4.6). The research objective was concluded with the limitations and possible problems with generic substitution as described in chapter 2, section 2.4.7 and 2.4.8.

6.2.2 Conclusions based on the empirical study

The following conclusions are based on the specific objectives of the empirical investigation.

The ***eighth specific research objective*** was to determine the overall cost and prescribing patterns of all medicine items on the database (refer to section 5.1.1.1), including cardiovascular, antihypertensive and ACE inhibitor items.

The percentages of the cardiovascular, antihypertensive and ACE inhibitor items and prescriptions as part of all prescriptions and items from the total database were discussed and summarised for the respective periods from 2001 until 2006. The contributions made by cardiovascular, antihypertensive and ACE inhibitor items as percentage of all medicine items decreased from 2004 until 2006. The total number of prescriptions and the total number of medicine items claimed through the database also showed a decrease from 2004 until 2006.

The fact that there was a reduction in the total number of prescriptions from 2004 to 2005 might be due to a reduction in the number of medical schemes from 80 in 2004 to 68 in 2005 and a further reduction from 35 medical schemes in 2006. The d-values calculated between the average cost per prescription containing cardiovascular, antihypertensive and ACE inhibitor items were of no practical significance. It was also concluded that the cost percentage of cardiovascular, antihypertensive and ACE inhibitor items as percentage of all medicine items decreased from 2004 until 2006 with 4.36%, 2.12% and 0.98% respectively. This might be due to the decrease in the number of prescriptions claimed from the database (refer to table 5.1.1) as well as the reduction in the average cost per item (refer to table 5.1).

The ***ninth specific research objective*** of the study was to determine the cost and overall prescribing patterns of innovator and generic products from the total database with reference to cardiovascular, antihypertensive and ACE inhibitor items (refer to section 5.1.3.2 and 5.1.3.3). The contribution made by cardiovascular innovator items to the total prevalence of all innovator items claimed decreased from 2004 until 2005 and decreased further from 2005 until 2006. The contribution made by cardiovascular generics to the total prevalence of all generic items claimed decreased from 2004 until 2005 and decreased further from 2005 until 2006. Antihypertensive innovator items represented 7.50% of all innovator items during 2001-2002 and decreased from 2004 until 2005 and decreased further from 2005 until 2006. The prevalence percentage of generic antihypertensive items increased from 2004 until 2005 and decreased from 2005 until 2006.

The prevalence percentage of ACE inhibitor innovators decreased with 0.66% (n=53292) from 2004 until 2005 and decreased with 0.25% (n=26678) from 2005 until 2006, and the ACE

inhibitor generics showed a decrease in prevalence percentage of 0.38% (n=25155) from 2004 until 2005 and a further decrease of 1.18% (n=22983) from 2005 until 2006. The fact that the period of 2001-2002 shows that the contribution made by innovators was consistently higher than that of generics, might be attributed to the fact that generic substitution was made compulsory by law in 2003 (also refer to chapter 2, section 2.4.5). It was further concluded from 2004 until 2006 the prevalence percentage with generic items was higher than that of innovators for cardiovascular and ACE inhibitor items. The number of cardiovascular, antihypertensive and ACE inhibitor innovator items was consistently higher than that of generic items. In contrast with this the contributions from the antihypertensive innovators were consistently higher from 2004 until 2006. This might be due to increased prescribing of generic items.

The contribution made by the cardiovascular innovator items to the total cost of all innovator items decreased from 2004 until 2006, and that of cardiovascular generic items to the total cost of generic items decreased from 2004 until 2006. The contribution of antihypertensive innovator items to the total cost of all innovator items showed a decrease from 2004 until 2006. The contribution of the antihypertensive generic items increased from 2004 until 2005 and decreased from 2005 until 2006. The contribution ACE inhibitor innovator items made to the total cost of all the innovator items decreased from 2004 until 2006.

The ***tenth specific research objective*** of the study was to determine the potential savings from cardiovascular, antihypertensive and ACE inhibitor item costs with regard to the single exit price (refer to section 5.1.3.3.1). It was concluded that cardiovascular and antihypertensive innovators showed the largest reduction in cost percentage of 23.36% and 24.31%, and cardiovascular, antihypertensive and ACE inhibitor generic items a reduction of 28.63%, 26.22% and 23.39% respectively during Sept 2004-Dec 2004, - except for ACE inhibitor innovators with the largest reduction in cost percentage of 26.67% during Sept 2005-Dec 2005. These reductions during 2004 might be attributed to the "full" implementation of the pricing regulations, and thus showing the lowest average cost per item (refer to table 5.2.10.1). In addition to this, only generic antihypertensive and ACE inhibitor items showed increases in cost percentage throughout 2006, with the highest increase during Sept 2006–Dec 2006. These increases might be attributed to the pricing regulation being declared invalid in September 2005 (refer to chapter 3, section 3.4.2.4). The average cost per ACE inhibitor item decreased by 12.86% (R24.02) from Jan 2004-Apr 2004 (phase before the pre implementation phase of the pricing regulations) until May-August (pre implementation phase of the pricing regulations). The average cost per ACE inhibitor item decreased by 27.92% (R52.14) from May-Aug 2004 (phase before the pre implementation phase of the pricing regulations) until Sept 2004-Dec 2004 ("full"

implementation phase of the pricing regulations). The total cost of cardiovascular ,antihypertensive and ACE inhibitor decreased between 25% and 30% between Sept 2004-Dec 2004 as shown in table 5.2.10.2 (refer to figure 3.3).

The ***eleventh specific research objective*** of the study was to investigate the prevalence of ACE inhibitor active ingredients (refer to section 5.2). It was concluded that the active ingredient with the highest prevalence percentage during 2001-2002 (including single as well as combination medicine items) was enalapril followed by perindopril. The two combination items with the highest prevalence percentages were quinapril/HCTZ followed by lisinopril/HCTZ. In 2004 and 2005 the highest prevalence percentages were again perindopril and indapamide/perindopril. As shown in figure 5.4 and appendix A, table A4 in 2006 the two active ingredients with the largest contribution were again perindopril and indapamide/perindopril. Both of these active ingredients showed a continuous increase in prevalence percentage from 2004 to 2006. The fact that some of the active ingredients showed decreases in prevalence percentages might be attributed to the reduction in the patients that received these items and/or the reduction in the number of prescriptions containing these items and/or the reduction in the number of medical schemes and/or the reduction in the number of medical aid members (due to the reduction in the number of medical schemes claimed through this medical scheme administrator).

The ***twelfth specific research objective*** of the study was to investigate the prevalence percentage by which ACE inhibitors form part of all the antihypertensive and cardiovascular items (refer to section 5.3 and 5.4). The contribution ACE inhibitors made to the total prevalence of all cardiovascular items showed an increase from 2004 until 2005 and a decrease from 2005 until 2006. The prevalence percentage stayed relatively stable between 26.28% and 24.84% from 2004 until 2006. The highest percentage contribution made by ACE inhibitors was during September 2004 until December 2004 and the smallest percentage contribution was made during May until August 2006. It was concluded that September 2004 until December 2004 showed the largest contribution made by ACE inhibitors as a percentage of antihypertensive items. September 2006-December 2006 showed the smallest contribution of ACE inhibitors to all antihypertensive items. The reasons are not clear and may be due to the change in treatment protocols, this however needs further investigation.

The ***thirteenth specific research objective*** of the study was to investigate the cost analyses of the top 20 ACE inhibitors according to prevalence (refer to section 5.5). The item with the highest CPI of all the items was Zestoretic® during 2004 and the item with the lowest CPI was

Pharmapress® 10mg during 2005 and 2006. This section further revealed that although the CPI's of generic equivalents were expected to be lower, there were products where the generic equivalents had higher CPI's than that of the innovators. This was due to the average cost per ACE inhibitor item of the generics being higher than that of the innovator equivalents such as Coversyl® and Prexum® as well as Coversyl Plus® and Prexum Plus®. Furthermore, it was concluded that Coversyl® as well as Coversyl Plus® was listed under the top 5 medicine items from 2001 until 2006, with Coversyl® (n=30031, CPI=1.09) and Coversyl Plus® (n=12378, CPI=1.21) for 2001-2002. During 2006 Coversyl® and Coversyl Plus® had prevalences of 3014 and 9161, as well as CPI's of 0.88 and 1.28 respectively . Prexum Plus® was only introduced into the market in 2006 and already it made it to the top 5 medicine items (n=9186) that same year with a CPI of 1.07. The fact that the above mentioned tradenames all contain either perindopril of indapamide/perindopril proved the wide use of these products. This was further illustrated by the fact that twelve out of the top 20 ACE inhibitor products in table 5.7 contained perindopril. Accuretic® 20/12.5mg only featured three times under the top 5 medicine items, Pharmapress Co® twice times, Tritace® 5mg, Zestoretic® 20/12.5mg and Preterax® were only listed once under the top 5 medicine items.

The ***fourteenth specific research objective*** of the study was to determine the prevalence and cost of the individual ACE inhibitor items (refer to section 5.6).

- **Benazepril** single item innovator items for the years 2001 until 2006 showed a continuous decrease in prevalence percentage from 2004 until 2006. Combination innovator items showed a continuous increase in prevalence percentage from 2004 until 2006. The total cost percentage of single item innovators showed a continuous decrease from 2004 until 2006, the total cost percentage of combination innovators a consistent increase from 2004 until 2006. The fact that benazepril combination items showed constant increases in prevalence might be explained by the advantages of using combination therapy (refer to chapter 2, section 2.3.3).
- **Captopril** containing single item innovators decreased in prevalence percentage from 2004 until 2006. The prevalence percentage of captopril containing single item generics showed a continuous decrease in prevalence percentage from 2004 until 2006. The prevalence of captopril containing generic items was consistently higher than the innovators; this might be due to mandatory generic substitution implemented in 2003 (refer to chapter 2, section 2.4.5). The prevalence percentage of captopril containing combination innovator items increased from 2004 until 2006. Captopril containing combination generic items also showed an increase 2004 until 2006. The total cost percentage of captopril containing single item innovators decreased from 2004 until 2006. The cost percentage of captopril containing

single item generics decreased consistently from 2004 until 2006. In addition to this the combination generic items also increased from 2004 until 2006.

- **Cilazapril** containing single item innovators showed a continuous decrease in prevalence percentage from 2004 until 2006. The prevalence of the combination innovator items increased from 2004 until 2006. In addition to this the prevalence contribution of the combination innovator items was higher than the single items during 2006. The results reveal an increased use in combination items from 2004 until 2006. The total cost percentage of cilazapril containing single items innovators decreased from 2004 until 2005 and then increased from 2005 until 2006. The total cost percentage by cilazapril containing combination innovators increased from 2004 until 2006.
- **Enalapril** containing single items innovators decreased from 2004 until 2006. The prevalence percentage of enalapril containing single item generics increased from 2004 until 2005 then decreased from 2005 until 2006. The prevalence of enalapril containing generic items were consistently higher than that of the innovator items. In addition to this the combination innovators showed a decrease from 2004 until 2006. The prevalence percentage of enalapril containing combination generic items showed an increase from 2004 until 2005 and then a decrease from 2005 until 2006. It can be concluded that the prevalence of enalapril containing combination generics also was consistently higher than the innovators from 2004 until 2006. This showed an increase in the use of enalapril containing items and might be due to the law making it mandatory for the pharmacist to inform the patient about generic substitution (also refer to chapter 2, section 2.4.5). Furthermore, the total cost contribution of enalapril containing single item innovators showed a decrease consistently from 2004 until 2006. The cost percentage of generic single items however increased from 2004 until 2006. It was further revealed that enalapril containing combination innovators showed a decrease from 2004 until 2006. Enalapril containing combination generic items showed an increase in cost contribution from 2004 until 2006.
- **Fosinopril** containing single item innovators increased in prevalence percentage from 2004 until 2005. The prevalence percentage then decreased from 2005 until 2006. Furthermore, the prevalence percentage of fosinopril containing combination innovator items showed a continuous decrease from 2004 until 2006. The decrease in prevalence from 2005 until 2006 might be attributed to the introduction of fosinopril containing single item generics. Fosinopril containing single innovator items increased from 2004 until 2005 and then decreased from 2005 until 2006. Fosinopril containing combination generic items showed a reduction from 2004 until 2006. The total cost percentage of fosinopril containing single innovator items increased from 2004 until 2005 and then decreased from 2005 until 2006. Fosinopril containing combination generic items showed a reduction in cost percentage from 2004 until

2005 and a further reduction from 2005 until 2006. In addition to this the prevalence and cost contribution was higher than that of fosinopril containing innovator items in September-December 2006.

- **Lisinopril** containing single items showed a decrease in the prevalence percentage from 2004 until 2006. Lisinopril containing generic single items also showed a continuous decrease from 2004 until 2006. Lisinopril containing combination innovator items showed a decrease from 2004 until 2006. Furthermore, May 2005 until August 2005 showed the introduction of lisinopril containing combination generic items and these items showed an increase in prevalence of from 2005 until 2006. The results further revealed that there was a decrease in the cost percentage of lisinopril containing single item innovators from 2004 until 2006. Lisinopril containing generic single items showed a decrease from 2004 until 2006. The total cost percentage of lisinopril containing combination innovator items decreased from 2004 until 2006. The combination generic items showed an increase from 2005 until 2006. It was concluded that although the cost and prevalence of single items and lisinopril containing combination innovator items decreased, lisinopril containing generic combination items showed an increase in prevalence and cost contribution since it was introduced during 2005.

- **Moexipril** containing innovators increased in prevalence of 83 items from 2004 until 2005 and then showed a decrease of 173 items from 2005 until 2006. Furthermore, the highest number of items claimed was from September 2004 until December 2004, which was during the "full" implementation of the single exit price (refer to chapter 3, section 3.4.2.3) and showed the lowest average cost per item (refer to Appendix B, table B7). It was further revealed that the total cost of all items containing moexipril increased from 2004 until 2005 and then decreased from 2005 until 2006.

- **Perindopril** containing single item innovator items showed a decrease from 2004 until 2006. Perindopril containing generic single items increased from 2004 until 2005 and then decreased from 2005 until 2006. The prevalence of the generic single items was consistently higher than that of the innovator items from 2004 until 2006. The perindopril containing combination innovator items showed a continuous increase from 2004 until 2006. Perindopril containing combination generic items was introduced into the market in 2005 and these items showed an increase in prevalence percentage from 2005 until 2006. Further the total cost percentage of perindopril containing single item innovators increased from 2004 until 2005 and then decreased by from 2005 until 2006. Perindopril containing generic single items showed an increase in cost percentage from 2004 until 2005 and a reduction from 2005 until 2006. Perindopril containing combination innovators consistently increased in cost percentage from 2004 until 2006. Perindopril containing combination generic items also

showed an increase in cost percentage 2005 until 2006. It can be concluded from this section that perindopril containing combination innovator items showed a consistently higher prevalence than the single items. This might be attributed to realisation of the advantages of using combination items.

- **Quinapril** containing combination innovator items showed a continuous increase in prevalence percentage from 2004 until 2006. The prevalence percentage of quinapril containing combination innovators items was consistently higher than that of quinapril containing single item innovators. The cost percentage of all quinapril containing single item innovators decreased from 2004 until 2006. The total cost percentage of quinapril containing combination item innovators showed an increase from 2004 until 2006. It can be concluded that quinapril containing generic items showed a continuous increase in prevalence percentage since it was introduced in 2006.
- **Ramipril** containing single item innovators decreased in prevalence percentage from 2004 until 2006. Ramipril containing generic single items however showed an increase in prevalence percentage from 2004 until 2006. In 2006 the prevalence percentage of ramipril containing single item generics was higher than that of the innovators, which showed an increase in the use of the generic items. The cost contribution made by ramipril containing single item innovators decreased from 2004 until 2006. Ramipril containing generic cost percentage was consistently lower than that of the innovator single items, but ramipril containing generic cost percentage showed an increase from 2004 until 2006.
- **Trandolapril** containing single item innovators decreased in prevalence percentage from 2004 until 2006. The combination innovator items increased in prevalence from 2004 until 2006. In addition to this the contributions of the combination items as well as the number of items were consistently higher than that of the single items. The contribution to the total cost of all trandolapril items decreased from 2004 until 2006. The combination items showed a constant increase in cost percentage from 2004 until 2006.

The ***fifteenth specific research objective*** of the study was to illustrate the new ACE inhibitors on the market (refer to section 5.6.2). The results revealed that of all the new trade names only 6.98% were single item innovators, 76.74% of the trade names were single item generics, 6.98% were combination item innovators and 9.30% were combination item generics. The fact that there was an increase in the different types of generic products increased the choices of using different generic products.

The ***sixteenth specific research objective*** of the study was to investigate the combination of ACE inhibitors and other antihypertensive products on the same prescription (refer to section 5.7). The number of prescriptions containing β-blockers with ACE inhibitors decreased continuously from 2004 until 2006. The prescriptions containing calcium channel blockers with ACE inhibitors increased from 2004 until 2006. In addition to this the number of times ACE inhibitors were prescribed together with other ACE inhibitors on the same prescription decreased from 2004 until 2005 and then increased from 2005 until 2006. It can be concluded that only the combination of ACE inhibitors with calcium-channel blockers showed an increase in percentage from 2004 until 2006. This increase might be attributed to the potential benefits of combining ACE inhibitors with calcium channel blockers (also refer to chapter 2, section 2.3.6.1).

Prescriptions containing an ACE inhibitor, a β-blocker and one other antihypertensive item, such as a diuretic or vasodilator decreased from 2004 until 2006. The prescriptions containing calcium channel blockers with an ACE inhibitor and one other antihypertensive item showed an increase in prevalence percentage from 2004 until 2006. Prescriptions with ACE inhibitors prescribed together with other ACE inhibitors and one other antihypertensive item showed an increase in prevalence percentage from 2005 until 2006. It can be concluded that the ACE inhibitors prescribed together with the calcium-channel blockers and one other antihypertensive item showed the higher contributions than the ACE inhibitor combinations with angiotensin antagonists or β-blockers (refer to chapter 2, section 2.3.6.1 for reasons of using calcium-channel blockers together with ACE inhibitors).

The prescriptions containing an ACE inhibitor with a β-blocker and two other antihypertensive items such as a diuretic or vasodilator decreased from 2004 until 2006. The number of times an ACE inhibitor and a calcium channel blocker were prescribed together with two other antihypertensive product increased by 8.11% from 2004 until 2005 and then decreased by 9.92% from 2005 until 2006. In addition to this the number of times an ACE inhibitor was prescribed together with another ACE inhibitor and two other antihypertensive items increased by 8.92% from 2004 until 2005 and then decreased to zero from 2005 until 2006. It was concluded that the combinations with calcium channel blockers were prescribed more than the other combinations with ACE inhibitors.

It was concluded that the prescriptions containing ACE inhibitors and β-blockers or angiotensin antagonists or calcium channel blockers or other ACE inhibitors and three other antihypertensive products showed decreases from 2004 until 2005. Furthermore, it can be added that the calcium-channel blocker combinations were prescribed more than the other combinations, and this might again be attributed to the benefits of using these combinations of ACE inhibitors and calcium channel blockers for the treatment of hypertension (refer to chapter

2, section 2.3.6.1). ACE inhibitors prescribed together with calcium-channel blockers were prescribed more throughout 2001 until 2006 than any other combination of ACE inhibitor and antihypertensive item.

The ***seventeenth specific research objective*** of the study was to investigate the number of prescriptions per patients containing at least one ACE inhibitor (refer to section 5.8). It can be concluded from section 5.8 that the number of patients claiming less than twelve prescriptions per year decreased constantly from 2004 until 2006, the percentage of patients claiming one prescription per year containing at least one ACE inhibitor increased constantly from 2004 until 2006 although the number of patients decreased constantly. The percentage of patients that claimed twelve prescriptions or less per year decreased from 2004 until 2005 and then increased from 2005 until 2006. Furthermore, the number of patients claiming more than twelve prescriptions per year containing at least one ACE inhibitor increased from 2004 until 2005 and then decreased from 2005 until 2006.The number of patients deemed compliant (claiming 80% or more of their prescriptions) showed a constant decrease from 2004 until 2006.

The ***eighteenth specific research objective*** of the study was to determine the prescribed daily dose and effect sizes between ACE inhibitor active ingredient innovators and generics (refer to section 5.9). The results revealed that for 2001-2002 the PDD established for an innovator as well as a generic had the lowest difference in PDD of 0.05mg/day between innovator and generic was for captopril 50mg and the highest difference was for enalapril 20mg of 1.40mg/day. During 2004 the PDD established for an innovator as well as a generic and the lowest difference in PDD of 0mg/day between innovator and generic was for enalapril 10mg and the highest difference was for captopril 12.5mg of 9.53mg/day. This was also the only active ingredient that showed a difference in dosing frequency between the innovator and generic products.

The results for 2005 revealed that the lowest difference in PPD for the innovators and generics was for lisinopril 5mg and the highest difference was by captopril/HCTZ 50/25mg for 2005. The period 2005 revealed the active ingredient for this period with the highest effect size was ramipril 1.25mg with (refer to chapter 4, section 4.8.2.5). For 2006 the biggest difference in PDD between the innovator and generic item was for captopril/HCTZ 50/25mg of 19.76mg/day and the smallest difference was for fosinopril 10mg and ramipril 2.5mg of 0.02mg/day. Captopril/HCTZ also showed the highest difference in PDD between innovator and generic during 2005, and therefore the difference in the prescribed daily dose between innovator and generic was the biggest for this active ingredient.

The ***nineteenth specific research objective*** of the study was to determine the ACE inhibitors on the list of top 50 products of Interpharm® Datasystems and comparing it to the ACE inhibitors on the list of top 50 products of Mediscor®, according to prevalence and cost (refer to section 5.10). The results from 2001-2002 revealed that the top 50 items according to total expenditure claimed through Mediscor® included four ACE inhibitors of which three are combination items and one a single agent. Interpharm® however only had two ACE inhibitors under the top 50 items. The item with the highest expenditure of the ACE inhibitors according to Mediscor® was Coversyl® 4mg in position 9, as well as according to Interpharm® in position 11.

For 2004 and according to total expenditure three ACE inhibitors (Coversyl Plus® , Coversyl® and Prexum®) were claimed according to Mediscor® as well as according to Interpharm®, and interestingly the same items claimed by Mediscor® were also claimed by Interpharm®. The item that contributed most to the total expenditure of both these two databases was the combination item, Coversyl Plus® in position 10 (Mediscor®) and position 8 (Interpharm®).

The data from 2005 revealed for the first time that two ACE inhibitors featured (according to total expenditure) under the top 50 except for Coversyl®, which did not appear in the top 50 of either Mediscor® or Interpharm®. With regard to Mediscor®, both Prexum® and Coversyl Plus® were at their highest positions on the top 50 list during 2006. It can therefore be concluded that for both databases, both of these items (Coversyl® and Prexum®), for the first time came in under the top 10. The results of 2006 revealed that Prexum® was at position 6 at Mediscor® according to total expenditure, which is the same position as 2005. Prexum® was at position 7 at Interpharm® which is 2 positions higher than 2005. It was concluded from 2006 that the ACE inhibitor generic items showed increases in expenditure and therefore moved up in the top 50 list according to total expenditure. The ACE inhibitor combination items (such as Coversyl Plus®) also showed increases in positions on the list for both Mediscor® and Interpharm® especially with the introduction of generic combination items such as Prexum Plus® . It was concluded from 2006 that the ACE inhibitor generic items showed increases in expenditure and therefore moved up on the top 50 list of both Mediscor® and Interpharm®. The ACE inhibitor combination items also showed improvements in positions on the list, especially with the introduction of generic combination items.

6.3 Limitations

The following limitations were identified throughout this study and are summarised below:

- Data from 2003 were not available in electronic format and therefore unavailable for use in this study.

- The data from the analyses were obtained from one medicine claims database, thus limiting external validity, implying that results can only be generalised to the specific database used.
- The data on the database were assumed to be correct.
- A valuable asset will be the availability of specific diagnoses such as ICD-10 codes or other scientific relevant diagnostic classification systems.

6.4 Recommendations

The following recommendations can be made for further studies:

- The availability of diagnoses as well as hospitalisation information to determine ACE inhibitor use and costs in specific diseases.
- Further possible cost savings with the use of generic substitution to be investigated.
- The usage of more than one medicine claims database to analyse cost and prevalence to be more representative of the South African private sector.
- A more detailed study to investigate combination therapy with other antihypertensive items with ACE inhibitors used for all of the indications of ACE inhibitors.

6.5 Chapter summary

In this chapter the conclusions, recommendations and limitations were discussed.

Bibliography

AMERICAN DIABETES ASSOCIATION. 2003. Treatment of hypertension in adults with diabetes. *Diabetes care,* 26 (Suppl.1):S80-S82.

ANDERSSON, F., CLINE, C., RYDEN-BERGSTEN, T. & ERHARDT, L. 1999. Angiotensin-converting enzyme (ACE) inhibitors in heart failure: the consequences of underprescribing. *Pharmacoeconomics,* 15:535-550.

ANTONELLI, I.R., PEDONE, C., PAHOR, M., ONDER, G., CARBONIN, P.U. 2002. Trends in prescribing ACE-inhibitors for congestive heart failure in elderly people. *Aging clinical and experimental research,* 14(6):516-521, Dec. Summary in Pubmed.

BAKRIS, G.L. 2003. High blood pressure. (*In* Beers, M.H., Fletcher, A.J., Jones, T.V., Porter, R., Berkwits, M. & Kaplan J.L., *eds.* The Merck manual of medical information. 2nd ed. Whitehouse Station, NJ: Merck Research Laboratories. p. 131-140.)

BARLO, K. 2007. Standard deviation. http://coe.sdsu.edu/eet/Articles/standarddev/start.htm Date of access: 15 Feb. 2007.

BEAUMONT, V. 2004. Summary of pricing regulations and provision for removal of discounting and bonusing. *Pharmaciae*, 12:24-25.

BECKER, R.J. 1990. Managed care is utilization review. *American journal of hospital pharmacy*, 27:2274-2276.

BEEVERS.G., LIP, Y.H. & O'BRIEN, E. 2001. ABC of hypertension: the pathophysiology of hypertension. http://www.bmj.com/cgi/content/full/322/7291/912 Date of access: 14 Aug. 2006.

BENOWITZ, N.L. 2001. Antihypertensive agents. (*In* Katzung, B.G., *ed.* Basic and clinical pharmacology. 8th ed. New York: McGraw-Hill. p. 155-180.)

BERECEK, K.H., KING, S.J. & WU, J.N. 1993. Angiotensin-converting enzyme and converting enzyme inhibitors. (*In* Raizada, M.K., Phillips, M.I. & Summers, C., *eds.* Cellular and molecular biology of the renin-angiotensin system. Boca Raton, FL: CRC Press. p.183-220.)

BESTER, M. & HAMMANN, E. 2005. Mediscor medicines review 2004. http://www.mediscor.net Date of access: 12 Jun. 2007.

BESTER, M. & HAMMANN, E. 2007. Mediscor medicines review 2006. http://www.mediscor.net Date of access: 18 Jun. 2007.

BESTER, M., BREWS, M. & HAMMANN, E. 2006. Medicines review 2005: mediscor pharmaceutical benefit management. http://www.mediscor.net Date of access: 14 Jun. 2007.

BESTER, M., VENTER, F., BROEKMAN, L., RADEMAN, C. FÜRST, W. HAMMAN, E. & PEREL, J. 2003. Mediscor medicines review 2002. http://www.mediscor.net Date of access: 20 Jun. 2007.

BICKET, D.P. 2002. Using ACE inhibitors appropriately. *American family physician*, 66:461-468.

BONK, R.J. 1999. Pharmacoeconomics in perspective. New York: Pharmaceutical Products Press. 116 p.

BOOTMAN, J.L., TOWNSEND, R.J. & MCGHAN, W.F. 1991. Introduction to pharmacoeconomics. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. Cincinnati, OH: Harvey Whitney Books. p. 3-17.)

BOOTMAN, J.L., TOWNSEND, R.J. & MCGHAN, W.F. 1996. Introduction to pharmacoeconomics. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. Cincinnati, OH: Harvey Whitney Books. p. 4-19.)

BRASE, C.H. & BRASE, C.P. 1999. Understandable statistics: concepts and methods. 6th ed. New York: Houghton Mifflin. 775 p.

BRASHERS, V.L., HAAK, S.W. & RICHARDSON, S.J. 1998. Alterations of cardiovascular function. (*In* McCance, K.L. & Huether, S.E., *eds.* Pathophysiology: the biologic basis of disease in adults and children. 3rd ed. St. Louis, MO: Mosby. p. 1024-1092.)

BROWN, M.J., CRUICKSHANK, J.K., DOMINICZAK, A.F., MACGREGOR, G.A., POULTER, N.R., RUSSELL, G.I., THOM, S. & WILLIAMS, B. 2003. Better blood pressure control: how to combine drugs. *Journal of human hypertension,* 17:81-86.

BROWN, N.J., DOUGLAS, E. & VAUGHAN, M.D. 1998. Angiotensin-converting enzyme inhibitors. *Circulation,* 97:1411-1420.

BUNDKIRCHEN, A. & SCHWINGER, R.H.G. 2004. Epidemiology and economic burden of chronic heart failure. *European heart journal*, (Suppl.D):D57-D60.

CANTOR, S.B. 2002. Pharmacoeconomics of coxib therapy. *Journal of pain and symptom management*, 24(1S):S28-S37.

CARTER, B.L. & SASEEN, J.J. 2002. Hypertension. (*In* Dipiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G. & Posey, L.M., *eds.* Pharmacotherapy: a pathophysiologic approach. 5th ed. New York: McGraw-Hill. p. 157-184.)

CENTER FOR DRUG EVALUATION AND RESEARCH. 2004. Generic drugs: questions and answers. http://www.fda.gov/cder/consumerinfo/generics_q&a.htm Date of access: 5 Sep. 2006.

CHOBANIAN, A.V., BAKRIS, G.L., BLACK, H.R., CUSHMAN, W.C., GREEN, L.A., IZZO, J.L., JONES, D.W., MATERSON, B.J., OPARIL, S., WRIGHT, J.T. & ROCCELLA, E.J. 2003. Seventh report of the national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*, 42:1206-1252.

CHRISCHILLES, E.A. 1996. Cost-effectiveness analysis. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 76-101.)

CHUI, M.A. & RUPP, M.T. 2000. Evaluation of online prospective DUR programs in community pharmacy practice. *Journal of managed care pharmacy*, 6:27-32.

COONS, S.J. & KAPLAN, R.M. 1996. Cost-utility analysis. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. Cincinnati, OH: Harvey Whitney Books. p. 102-127.)

COOPER, R. & ROTIMI, C. 1997. Hypertension in blacks. *American journal of hypertension*, 10:804-812.

COUNCIL FOR MEDICAL SCHEMES. 2003. Hypertension. http://www.medicalschemes.com/Publications/ZipPublications/Prescribed%20Minimum%Benefits/Hypertension.pdf. Date of access: 2 Jun. 2007.

DAVIES, M.K., GIBBS, C.R. & LIP, G.Y.H. 2000. ABC of heart failure: management: diuretics, ACE inhibitors, and nitrates. *British medical journal,* 320:428-431.

DEPARTMENT OF HEALTH **see** SOUTH AFRICA. Department of Health.

DIABETES IN CONTROL.COM. 2006. New UK research indicates that taking beta-blocker drugs to treat high blood pressure can increase the risk of developing diabetes by 50 percent, compared to newer drugs. http://www/diabetesincontrol.com/results.php?storyarticle=4231 Date of access: 14 Jun. 2007.

DRUMMOND, M.F., O'BRIEN, B., STODDART, G.L. & TORRANCE, G.W. 1997. Methods for the economic evaluation of health care programmes. 2nd ed. New York: Oxford University Press. 305 p.

ENRIGHT, S.M. & FLAGSTAD, M.S. 1991. Quality and outcome: pharmacy's professional imperative. *American journal of hospital pharmacy*, 48:1908-1911.

EPSTEIN, M. & BAKRIS, G. 1996. Newer approaches to antihypertensive therapy: use of fixed-dose combination therapy. *Archives of internal medicine,* 156:1969-1978.

ERWIN, W.G. 1991. The definition of drug utilization review: statement of issues. *Clinical pharmacology and therapeutics*, 50:596-599.

EUROPEAN SOCIETY OF HYPERTENSION. 2003. European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of hypertension,* 21:1011-1053.

FAIRFIELD, G., HUNTER, D.J., MECHANIC, D. & ROSLEFF, F. 1997. Managed care: origins, principles, and evolution. *British medical journal*, 314:1823-1826.

FALKNER, B. & SADOWSKI, R.H. 1995. Hypertension in children and adolescents. *American journal of hypertension*, 8:106S-110S.

FINK, G.D. 1998. Antihypertensive drugs. (*In* Brody, T.M., Larner, J. & Minneman, K.P., *eds.* Human pharmacology: molecular to clinical. 3rd ed. St. Louis, MO: Mosby. p. 181-194.)

FREE MARKET FOUNDATION. 2006. Comment to the Department of Health in response to Government Gazette No. 28214 of 11 November 2005 (Notice No 2007 of 2005): Comments on an increase in the Single Exit Price of medicines in terms of Regulation 8(1) of the above mentioned regulations. http://www.freemarketfoundation.com/htmupload/PUBDoc1179.pdf Date of access: 12 Apr. 2007.

GARATTINI, S & TOGNONI, G. 1993. Drug utilization review and pharmacoeconomics: interaction after parallel development? *Pharmacoeconomics*, 4:162-172.

GAZIANO, T.A., STEYN, K., COHEN, J.D., WEINSTEIN, M.C. & OPIE, L.H. 2005. Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood pressure level. *Circulation,* 112:3569-3576.

GIBBON, C.J., *ed.* 2003. South African medicines formulary. 6th ed. Cape Town: The South African Medical Association. 569 p.

GIBBON, C.J., *ed.* 2005. South African medicines formulary. 7th ed. Cape Town: The South African Medical Association. 581 p.

GIBBS, C.R., BEEVERS, D.G. & LIP, G.Y.H. 1999. The management of hypertensive disease in black patients. *Quarterly journal of medicine*, 92:187-192.

GLOBAL HEALTH MEDICAL SCHEME. 2007. Chronic medication: questions and answers. http://www.globalhealth.co.za/content/munimag/june_2007/chronic.html Date of access: 15 Oct. 2007.

HANSSON, L. & HIMMELMANN, A. 1994. Combination therapy in the treatment of hypertension. (*In* Swales, J.D., *ed.* Textbook of hypertension. Oxford: Blackwell Scientific Publications. p. 1142-1148.)

HEALTH CARE FINANCING ADMINISTRATION. 1996. Medicare :managed care. http://www.pueblo.gsa.gov/cic_text/fed_prog/mm_care/medcare.htm Date of access: 2 Apr. 2007.

HOPE, E. 2006. Beta-blockers 'increase diabetes risk by 50 percent'. http://www.pindolol.com/news_article/?tx_ttnews%5Btt_news%5D=10&tx_ttnews%5Bba... Date of access: 30 Mar. 2007.

HUNT, S.A., ABRAHAM, W.T., CHIN, M.H., FELDMAN, A.M., FRANCIS, G.S., GANIATS, T.G., JESSUP, M., KONSTAM, M.A., MANCINI, D.M., MICHL, K., OATES, J.A., RAHKO, P.S., SILVER, M.A., STEVENSON, L.W. & YANCY, C.W. 2005. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult-summary article. *Journal of the American College of Cardiology*, 46:1116-1143.

HUNT, S.A., BAKER, D.W., CHIN, M.H., CINQUEGRANI, M.P., FELDMANMD, A.M., FRANCIS, G.S., GANIATS, T.G., GOLDSTEIN, S., GREGORATOS, G., JESSUP, M.L., NOBLE, R.J., PACKER, M., SILVER, M.A., STEVENSON, L.W., GIBBONS, R.J., ANTMAN, E.M., ALPERT, J.S., FAXON, D.P., FUSTER, V., JACOBS, A.K., HIRATZKA, L.F., RUSSELL, R.O. & SMITH, S.C. 2001. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/ American Heart Association task force on practice guidelines. *Circulation*, 104:2996-3007.

IGLEHART, J.K. 1994. Physicians and the growth of managed care: health policy report. *New England journal of medicine,* 331:1167-1171.

INESTA, A. 1992. Drug utilization in community pharmacy. *Journal of clinical pharmacy and therapeutics*, 17:353-355.

IVES, H.E. 2001. Diuretic agents. (*In* Katzung, B.G., *eds.* Basic and clinical pharmacology. 8th ed. New York: McGraw-Hill. p. 245-264.)

JACKSON, E.K. & GARRISON, J.C. 1996. Renin and angiotensin. (*In* Hardman, J.G. & Limbird, L.E., *eds.* Goodman & Gilman's: the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill. p. 733-758.)

JACKSON, G., GIBBS, C.R., DAVIES, M.K. & LIP, G.Y.H. 2000. ABC of heart failure: pathophysiology. *British medical journal,* 320:167-170.

JAISINGH, L.R. 2000. Statistics for the utterly confused. New York : McGraw-Hill. 318 p.

JOHNSON, J.A., PARKER, R.B. & PATTERSON, J.H. 2002. Heart failure. (*In* Dipiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G. & Posey, L.M., *eds.* Pharmacotherapy: a pathophysiologic approach. 5th ed. New York: McGraw-Hill. p. 185-218.)

JOHNSTON, C.I. 1989. Angiotensin-converting enzyme inhibitors: differences and advantages for first line therapy in hypertension. *Clinical and experimental hypertension*, 11:1097-1115.

JULIUS, S. 2000. Worldwide trends and shortcomings in the treatment of hypertension. *American journal of hypertension*, 13:57S-61S.

KAPLAN, N.M. 2001. Low-dose combination therapy: the rationalization for an ACE inhibitor and a calcium channel blocker in higher risk patients. *American journal of hypertension*, 14:8S-11S.

KATZUNG, B.G. & PARMLEY, W.W. 2001. Cardiac glycosides & other drugs used in congestive heart failure. (*In* Katzung, B.G., *ed.* Basic and clinical pharmacology. 8th ed. New York : McGraw-Hill. p. 200-218.)

KELLER, G. & WARRACK, B. 2000. Statistics for management and economics. 5th ed. Pacific Grove: Duxbury Press. 901 p.

KIRKWOOD, B.R. 1988. Essentials of medical statistics. London: Blackwell Science. 234 p.

KRELING, D.H. & MOTT, D.A. 1993. The cost-effectiveness of drug utilization review in an outpatient setting. *Pharmacoeconomics*, 4:414-436.

LARSON, L.N. 1996. Cost determination and analysis. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds*. Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 44-59.)

LEE, D. & BERGMAN, U. 1994. Studies in drug utilization (*In* Strom. B.L., *ed.* Pharmacoepidemiology. 2nd ed. Chichester : Wiley. p. 379-394.)

LEMOGOUM, D., SEEDAT, Y.K., MABADEJE, A.F.B., MENDIS, S., BOVET, P., ONWUBERE, B., BLACKETT, K.N., LENFANT, C., KABANGU, J.R.M., BLOCK, P., BELHOCINE, M. & DEGAUTE, J.P. 2003. Recommendations for prevention, diagnosis and management of hypertension and cardiovascular risk factors in sub-Saharan Africa. *Journal of hypertension*, 21:1993-2000.

LIPTON, H.L. & BIRD, J.A. 1993. Drug utilization review in ambulatory settings: state of the science and directions of outcomes research. *Medical care*, 31:1069-1082.

LUMA, G.B. & SPIOTTA, R.T. 2006. Hypertension in children and adolescents. *American family physician*, 73:1158-1168.

MAGILL, M.K., GUNNING, K., SAFFEL-SHRIER, S. & GAY, C. 2003. New developments in the management of hypertension. *American family physician*, 68:853-858.

MASOUDI, F.A., RATHORE, S.S., WANG, Y., HAVRANEK, E.P., CURTIS, J.P., FOODY, J.M. & KRUMHOLZ, H.M. 2004. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation,* 110:724-731.

MASSIE, B.M. 2004. Systemic hypertension. (*In* Tierney, L.M., McPhee, S.J. & Papadakis, M.A., *eds.* Current medical diagnosis & treatment. 43th ed. London: Appleton & Lange. p. 401-427.)

MASSIE, B.M. & AMIDON, T.M. 2004. Heart. (*In* Tierney, L.M., McPhee, S.J. & Papadakis, M.A., *eds.* Current medical diagnosis & treatment. 43th ed. London: Appleton & Lange. p. 306-400.)

MCGHAN, W.F. & KITZ, D.S. 1996. Cost-benefit analysis. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 60-75.)

MCKUSICK, V.A. 2007. Angiotensin I-converting enzyme; ACE. http:www.ncbi.nlm.gov/sites/entrez?cmd=Retrieve&db=OMIM&dopt=Detailed&t... Date of access: 2 Jun. 2007.

MCMURRAY, J.J.V., MCGUIRE, A., DAVIE, A.P. & HUGHES, D. 1997. Cost-effectiveness of different ACE inhibitor treatment scenarios post-myocardial infarction. *European heart journal,* 18:1411-1415.

MESTERN, A. 2003. Article on generic medicine. *BP Southern Africa Medical Aid Society: newsletter.* http://www.mhg.co.za/SchemeSites/docs/bp/news/november_2003.pdf Date of access: 13 Jun. 2007.

MILNE, F.J. & PINKNEY-ATKINSON, V.J. 2004. Hypertension guideline 2003 update. *South African medical journal,* 94:209-225.

MOORE, J. 2005. Hypertension: catching the silent killer. *The nurse practitioner*, 30(10):16-37, Oct.

MOSER, M. & BLACK, H.R. 1998. The role of combination therapy in the treatment of hypertension. *American journal of hypertension,* 11:73S-78S.

MOTT, D.A. & CLINE, R.R. 2002. Exploring generic drug use behaviour: the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution. *Medical care,* 40:662-674.

NAVOOKARASU, N.T., RAHMAN, A.R. & ABDULLAH, I. 1999. First-dose response to angiotensin-converting enzyme inhibition in congestive heart failure a Malaysian experience. *International journal of clinical practice*, 53:25-30.

NATIONAL DRUG POLICY FOR SOUTH AFRICA. **see** SOUTH AFRICA. Department of Health.

NEUTEL, J.M., SMITH, D.H.G. & WEBER, M.A. 2001. Low-dose combination therapy: an important first-line treatment in the management of hypertension. *American journal of hypertension,* 14:286-292.

NORDMANN, A.J., KRAHN, M., LOGAN, A.G., NAGLIE, G. & DETSKY, A.S. 2003. The cost-effectiveness of ACE inhibitors as first-line antihypertensive therapy. *Pharmacoeconomics*, 21:573-585.

OATES, J.A. 1996. Drugs used for the treatment of myocardial ischemia. (*In* Hardman, J.G. & Limbird, L.E., *eds.* Goodman & Gilman's: the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill. p. 781-808.)

O'BRIEN, A.A.J. & BULPITT, C.J. 1997. Hypertensive disease. (*In* Speight, T.M. & Holford, N.H.G., *eds.* Avery's drug treatment. 4th ed. Auckland: Adis International. p. 897-932.)

OPIE, L.H. 1992. Angiotensin converting enzyme inhibitors, scientific basis for clinical use. New York: Wiley-Liss. 266 p.

OSMAN, L. 2004. Regulations relating to the transparent pricing system for medicines. http://www.edoc.co.za/modules.php?name=News&file=article&sid=729 Date of access: 15 Nov. 2006.

OSTERHAUS, J.T. & DRAUGALIS, J.R. 1991. Application of pharmacoeconomics for drug therapy decisions. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. Cincinnati, OH: Harvey Whitney Books. p. 134-145.)

PERLOFF, D., GRIM, C., FLACK, J., FROHLICH, E.D., HILL, M., MCDONALD, M. & MORGENSTERN, B.Z. 1993. Human blood pressure determination by sphygmomanometry. *Circulation,* 88:2460-2470.

PORTH, M.C. 1998. Alterations in blood pressure: hypertension and orthostatic hypotension. (*In* Porth, M.C., *ed.* Pathophysiology: concepts of altered health states. 5th ed. Philadelphia: Lippincott. p. 363-384.)

PRESCRIPTION PRICING AUTHORITY. 2004. Cardiovascular prescribing. http://www.ppa.org.uk/news/pact-052004.htm [Date of access: 3 Feb. 2006]

PRINEAS, R.J. & SINAIKO, A.R. 1994. Hypertension in children. (*In* Swales, J.D., *ed.* Textbook of hypertension. Oxford: Blackwell Scientific Publications. p. 750-766.)

ROBERTSON, R.M. & ROBERTSON, D. 1996. Drugs used for the treatment of myocardial ischemia. (*In* Hardman, J.G. & Limbird, L.E., *eds.* Goodman & Gilman's: the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill. p. 759-780.)

ROGNEHAUGH, R. 1998. The managed health care dictionary. 2nd ed. Gaithersburg: Aspen Publishers. 216 p.

ROSNER, F. 2006. Patient non-compliance: causes and solutions. *The Mount Sinai journal of medicine*, 73:553-559.

ROTHBERG, A., MAGENNIS, R. & MYNHART, S. 1999? Managed health care. http://www.hst.org.za/uploads/files/chapter4_99.pdf Date of access: 7 Nov. 2006.

RYLANCE, P.B. 1995. Hypertension. (*In* Phillps, J., Murray, P. & Crocker, J., *eds.* The biology of disease. Cambridge, MA: Blackwell Science: Excel Typesetters. p. 190-197.)

SA **see** SOUTH AFRICA.

SACRISTAN, J.A. & SOTO, J. 1994. Drug utilization studies as tools in health economics. *Pharmacoeconomics*, 5: 299-312.

SANCHEZ, L.A. 1996. Appendix. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 290-302.)

SAS FOR WINDOWS 9.1. 2006. SAS Institute Inc., 2002-2003.

SASEEN, J.J. & CARTER, B.L. 2005. Hypertension. (*In* DiPiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G. & Posey, L.M., *eds.* Pharmacotherapy: a pathophysiologic approach. 6thed. New York: McGraw-Hill. p. 185-215.)

SCHULMAN, K.A. 1996. Pharmacoeconomics and clinical practice: a physician's view. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 258-277.)

SCHWINGHAMMER, T.L. 2003a. Heart failure. (*In* Wells, B.G., Dipiro, J.T., Schwinghammer, T.L. & Hamilton, C.W., *eds.* Pharmacotherapy handbook. 5th ed. New York: McGraw-Hill. p. 56-70.)

SCHWINGHAMMER, T.L. 2003b. Hypertension. (*In* Wells, B.G., Dipiro, J.T., Schwinghammer, T.L. & Hamilton, C.W., *eds.* Pharmacotherapy handbook. 5th ed. New York: McGraw-Hill. p. 83-98.)

SEEDAT, Y.K., CROASDALE, M.A., MILNE, F.J., OPIE, L.H., PINKNEY-ATKINSON, V.J., RAYNER, B.L. & VERIAVA, Y. 2006. South African hypertension guideline 2006. *South African medical journal,* 96:337-360.

SELETSWANE, D.P. 2004. Usage patterns and cost analysis of angiotensin-converting enzyme (ACE) inhibitors using a medical aid claims database. Potchefstroom : NWU. (Dissertation – M.Pharm.) 145 p.

SERFONTEIN, C.B. 1996. Drug utilization review: a third party payers perspective. Potchefstroom: PU vir CHO. (Thesis – M.Pharm.) 217 p.

SERFONTEIN, J.H.P. 1989. Medisyne verbruik in provinsiale hospitale met besondere verwysing na die rol van die apteker in die beheerproses. Potchefstroom: PU vir CHO. (Thesis-D.Pharm.) 417 p.

SJÖQVIST, F. & BIRKETT, D. 2003. Drug utilization. http://www.iuphar.org/pdf/hum_76.pdf Date of access: 28 Sep. 2006.

SNYMAN, J.R., *eds.* 2005. MIMS monthly index of medical specialities. Pretoria: MIMS. 391 p.

SOUTH AFRICA. Department of Health. 1996. National drug policy for South Africa. Pretoria: Goverment Printer. 28 p.

SOUTH AFRICA. 2003. PSSA pharmacy law compendium. Durban: LexisNexisButterworths.

SOUTH AFRICA. Department of Health. 2003. South African standard treatment guidelines and essential drug list for primary health care. Pretoria: Government Printer. 365 p.

SOUTH AFRICA. 2004. Regulations relating to a transparent pricing system for medicines and scheduled substances. *Government gazette*, 26304:466, 30 Apr. (Regulation gazette no. 7956.)

SOUTH AFRICA. 2006. Regulations relating to a transparent pricing system for medicines and scheduled substances: methodology for international benchmarking of the prices of medicines and scheduled substances in South Africa. *Government gazette*, 29443:1211, 1 Dec.

STERACHIS, A., SULLIVAN, S.D. & PENNA, P.M. 1996. The applications of Pharmacoeconomics in managed health care settings. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney Books. p. 242-257.)

STEYN, H.S. 1999. Praktiese beduidenheid: die gebruik van effekgrootes. Potchefstroom : PU vir CHO. 28 p.

STEYN, K., GAZIANO, T.A., BRADSHAW, D., LAUBSHER, R. & FOURIE, J. 2001. Hypertension in South African adults: results from the demographic and health survey, 1998. *Journal of hypertension,* 19:1717-1725.

STRUWIG, V. 2001. Introduction to pharmacoeconomics (FPHA 611). Potchefstroom: PU vir CHO. 167 p. (Dictation)

STRUWIG, V.A. 1997. A South African model for the cost-justification of new pharmaceuticals. Potchefstroom: PU vir CHO. (Thesis- Ph.D.) 247 p.

SZUCS, T.D. 1997. Pharmacoeconomics of angiotensin converting enzyme inhibitors in heart failure. *American journal of hypertension,* 10:272S-279S.

TALHEIMER, W. & COOK, S. 2002. How to calculate effect sizes from published research: a simplified methodology. http://www.work-learning.com/Catalog/index.htm. Date of access: 15 Feb. 2007.

THE ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY. 1999? Generic medicines. http://www.abpi.org.uk/publications/briefings/generics.pdf. Date of access: 1 Sep. 2006.

TODD, M.W., KEITH, T.D. & FOSTER, M.T. 1987. Development and implementation of a comprehensive, criteria-based drug-use review program, *American journal of hospital pharmacy*, 44:529-535.

TREVOR, A.J., KATZUNG, B.G. & MASTERS, S.B. 2002. Pharmacology: examination & board review. 6th ed. New York: McGraw-Hill. 662 p.

TRUTER, I. 1994. A drug utilization study to establish norms for rational and cost-effective use of medicine. Port Elizabeth: UPE. (Dissertation – M.Sc.) 329 p.

TRUTER, I. 1995. Drug utilization research: the future for health care analysis in South Africa. *South African pharmaceutical journal*, 62:338-339.

TRUTER, I. 1997. Opposite sides of the same coin? Pharmacoeconomics and drug utilization. *South African pharmaceutical journal*, 64:19-20.

TSHABALALA-MSIMANG, M. 2004. Finalisation of regulations on medicine pricing. *Pharmaciae,* 12:5-6.

TSHABALALA-MSIMANG, M. 2006. Announcement of the new dispensing fee for medicine. http://www.doh.gov.za/docs/sp/2006/sp1031.html Date of access: 26 Mar. 2007.

WEBER, A.M. 1998. Unsolved problems in treating hypertension: rationale for new approaches. *American journal of hypertension*, 11:145S-149S.

WHO **see** WORLD HEALTH ORGANIZATION.

WILLIAMS, B., POULTER, N.R., BROWN, M.J., DAVIS, M., MCINNES, G.T., POTTER, J.F., SEVER, P.S. & THOM, S.G. 2004. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004. *Journal of human hypertension,* 18:139-185.

WONG, J., PATEL, R.A. & KOWEY, P.R. 2004. The clinical use of angiotensin-converting enzyme inhibitors. *Progress in cardiovascular diseases,* 47:116-130.

WORLD HEALTH ORGANIZATION. International Society of Hypertension Writing Group. 2003a. World Health Organisation (WHO)/International Society of Hypertension (ISH) statement on the management of hypertension. *Journal of hypertension,* 21:1983-1992.

WORLD HEALTH ORGANIZATION. 2003b. Introduction to drug utilization research. http://www.who.int/entity/medicines/areas/quality_safety/safety_efficacy/Drug%20utilization%research.pdf Date of access: 20 Jun. 2007.

Appendix A

Table A1: Frequency of active ingredients for the year 2001-2002

Period	Description	Frequency (N)	Percentage (%) of all ACE inhibitors
Year 2001-2002	Enalapril	30248	15.21
	Perindopril	30031	15.10
	Ramipril	22688	11.41
	Lisinopril	20690	10.40
	Quinapril/HCTZ	15839	7.96
	Lisinopril/HCTZ	14371	7.22
	Enalapril/HCTZ	12389	6.23
	Indapamide/Perindopril	12378	6.22
	Captopril	10925	5.49
	Quinapril	8954	4.50
	Felodipine/Ramipril	5055	2.54
	Trandolapril/Verapamil	4160	2.09
	Captopril/HCTZ	2627	1.32
	Fosinopril	2347	1.18
	Trandolapril	1707	0.86
	Cilazapril	1586	0.80
	Cilazapril/HCTZ	1225	0.62
	Fosinopril/HCTZ	1025	0.52
	Benazepril	387	0.19
	Benazepril/HCTZ	280	0.14
	Moexipril	9	0.00
	Total	**198921**	**100.00**

Table A2: Frequency of active ingredients for the year 2004

Period	Description	Frequency (N)	Percentage (%)* of all ACE inhibitors
Year 2004	Perindopril	33752	18.34
	Indapamide/Perindopril	27337	14.86
	Enalapril	26357	14.32
	Lisinopril	16971	9.22
	Ramipril	16594	9.02
	Enalapril/HCTZ	12603	6.85
	Quinapril/HCTZ	11149	6.06
	Lisinopril/HCTZ	8382	4.55
	Captopril	6903	3.75
	Felodipine/Ramipril	5845	3.18
	Quinapril	5530	3.01
	Trandolapril/Verapamil	3628	1.97
	Captopril/HCTZ	2225	1.21
	Fosinopril	1387	0.75
	Cilazapril	1236	0.67
	Trandolapril	957	0.52
	Cilazapril/HCTZ	923	0.50
	Fosinopril/HCTZ	870	0.47
	Moexipril	791	0.43
	Benazepril	368	0.20
	Benazepril/HCTZ	209	0.11
	Ramipril/HCTZ	1	0.00
	Total	**184018**	**99.99**

* The sum of the percentage column does not amount to 100 due to the fact that the percentages were rounded of to two decimals

Table A3: Frequency of active ingredients for the year 2005

Period	Description	Frequency (N)	Percentage (%)* of all ACE inhibitors
Year 2005	Perindopril	26355	24.96
	Indapamide/Perindopril	23856	22.60
	Enalapril	12808	12.13
	Ramipril	7010	6.64
	Enalapril/HCTZ	6602	6.25
	Lisinopril	6594	6.25
	Quinapril/HCTZ	5047	4.78
	Lisinopril/HCTZ	3144	2.98
	Felodipine/Ramipril	3128	2.96
	Trandolapril/Verapamil	2487	2.36
	Captopril	2191	2.08
	Quinapril	1933	1.83
	Captopril/HCTZ	1393	1.32
	Moexipril	874	0.83
	Trandolapril	579	0.55
	Fosinopril	478	0.45
	Cilazapril	303	0.29
	Cilazapril/HCTZ	287	0.27
	Fosinopril/HCTZ	210	0.20
	Benazepril/HCTZ	178	0.17
	Benazepril	114	0.11
	Total	**105571**	**100.01**

* The sum of the percentage column does not amount to 100 due to the fact that the percentages were rounded of to two decimals

Table A4: Frequency of active ingredients 2006

Period	Description	Frequency (N)	Percent (%)* of all ACE inhibitors
Year 2006	Indapamide/Perindopril	20257	36.23
	Perindopril	17570	31.43
	Enalapril	3492	6.25
	Ramipril	2774	4.96
	Enalapril/HCTZ	1734	3.10
	Felodipine/Ramipril	1548	2.77
	Lisinopril/HCTZ	1532	2.74
	Trandalopril/Verapamil	1505	2.69
	Quinapril/HCTZ	1385	2.48
	Lisinopril	983	1.76
	Moexipril	701	1.25
	Captopril/HCTZ	606	1.08
	Captopril	397	0.71
	Quinapril	396	0.71
	Quinapril/HCTZ	380	0.68
	Trandalopril	234	0.42
	Benazepril/HCTZ	160	0.29
	Fosinopril	89	0.16
	Cilazapril/HCTZ	48	0.09
	Benazepril	45	0.08
	Cilazapril	44	0.08
	Fosinopril/HCTZ	30	0.05
	Total	**55910**	**100.01**

* The sum of the percentage column does not amount to 100 due tot the fact that the percentages were rounded of to two decimals.

Appendix B

Table B1: Cost and prevalence of Benazepril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single	**Benazepril**	Cibace® 10mg	275	71.06	162.68	17.79	44 737.03
				Cibace® 20mg	76	19.64	276.29	43.80	20 998.00
				Cibace® 5mg	36	9.30	140.31	48.10	5 051.11
				Total	**387**	**100.00**	**182.91**	**54.63**	**70 786.14**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	280	100.00	268.77	45.71	75 256.95
				Total	**280**	**100.00**	**268.77**	**45.71**	**75 256.95**
Year 2004	Innovator	Single agent	**Benazepril**	Cibace® 10mg	213	57.88	141.26	59.98	30 088.87
				Cibace® 20mg	87	23.64	261.32	43.80	22 734.88
				Cibace® 5mg	68	18.48	134.44	23.38	9 141.95
				Total	**368**	**100.00**	**168.39**	**72.91**	**61 965.70**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	209	100.00	284.02	51.95	59 359.27
				Total	**209**	**100.00**	**284.02**	**51.95**	**59 359.27**
Year 2005	Innovator	Single agent	**Benazepril**	Cibace® 10mg	63	55.26	149.58	51.56	9 423.37
				Cibace® 5mg	36	31.58	132.90	11.58	4 784.57
				Cibace® 20mg	15	13.16	251.40	23.08	3 770.94
				Total	**114**	**100.00**	**157.71**	**54.44**	**17 978.88**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	178	100.00	272.67	53.42	48 534.86
				Total	**178**	**100.00**	**272.67**	**53.42**	**48 534.86**

Table B1 (continued): Cost and prevalence of Benazepril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Single agent	**Benazepril**	Cibace® 10mg	26	57.78	170.25	32.44	4 426.60
				Cibace® 5mg	19	42.22	156.13	43.94	2 966.46
				Total	**45**	**100.00**	**164.29**	**37.91**	**7 393.06**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	160	100.00	42.40	297.41	45 787.37
				Total	**160**	**100.00**	**286.17**	**42.40**	**45 787.37**
Jan - Apr 2004	Innovator	Single agent	**Benazepril**	Cibace® 10mg	62	57.41	145.19	82.19	9 001.85
				Cibace® 20mg	28	25.93	301.60	6.16	8 444.82
				Cibace® 5mg	18	16.67	137.28	29.83	2 471.03
				Total	**108**	**100.01**	**184.42**	**94.13**	**19 917.70**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	50	100.00	286.00	55.75	14 300.02
				Total	**50**	**100.00**	**286.00**	**55.75**	**14 300.02**
May - Aug 2004	Innovator	Single agent	**Benazepril**	Cibace® 10mg	70	56.00	147.25	61.93	10 307.22
				Cibace® 20mg	29	23.20	266.49	16.20	7 728.30
				Cibace® 5mg	26	20.80	138.82	25.09	3 609.34
				Total	**125**	**100.00**	**173.16**	**70.60**	**21 644.86**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	85	100.00	295.47	31.22	25 114.82
				Total	**85**	**100.00**	**295.47**	**31.22**	**25 114.82**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B1 (continued): Cost and prevalence of Benazepril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep- Dec 2004	Innovator	Single agent	**Benazepril**	Cibace® 10mg	81	60.00	133.08	31.08	10 779.80
				Cibace® 20mg	30	22.22	218.73	43.95	6 561.76
				Cibace® 5mg	24	17.78	127.57	13.16	3 061.58
				Total	**135**	**100.00**	**151.13**	**48.41**	**20 403.14**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	74	100.00	269.52	64.14	19 944.43
				Total	**74**	**100.00**	**269.52**	**64.14**	**19 944.43**
Jan - Apr 2005	Innovator	Single agent	**Benazepril**	Cibace® 10mg	21	53.85	145.07	45.38	3 046.37
				Cibace® 5mg	11	28.21	130.52	12.69	1 435.67
				Cibace® 20mg	7	17.95	259.00	33.42	1 813.02
				Total	**39**	**100.01**	**161.41**	**59.00**	**6 295.06**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	56	100.00	271.40	55.13	15 198.23
				Total	**56**	**100.00**	**271.40**	**55.13**	**15 198.23**
May - Aug 2005	Innovator	Single agent	**Benazepril**	Cibace® 10mg	21	56.76	153.66	55.97	3 226.90
				Cibace® 5mg	12	32.43	133.64	11.55	1 603.72
				Cibace® 20mg	4	10.81	244.74	0.00	978.96
				Total	**37**	**100.00**	**157.02**	**53.15**	**5 809.58**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	60	100.00	270.85	57.31	16 251.02
				Total	**60**	**100.00**	**270.85**	**57.31**	**16 251.02**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B1 (continued): Cost and prevalence of Benazepril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Single agent	**Benazepril**	Cibace® 10mg	21	55.26	150.00	54.86	3 150.10
				Cibace® 5mg	13	34.21	134.24	11.27	1 745.18
				Cibace® 20mg	4	10.53	244.74	0.00	978.96
				Total	**38**	**100.00**	**154.59**	**52.00**	**5 874.24**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	62	100.00	275.57	48.48	17 085.61
				Total	**62**	**100.00**	**275.57**	**48.48**	**17 085.61**
Jan - Apr 2006	Innovator	Single agent	**Benazepril**	Cibace® 5mg	10	58.82	169.33	58.76	1 693.30
				Cibace® 10mg	7	41.18	168.34	0.00	1 178.38
				Total	**17**	**100.00**	**168.92**	**44.07**	**2 871.68**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	54	100.00	290.70	54.68	15 697.86
				Total	**54**	**100.00**	**290.70**	**54.68**	**15 697.86**
May - Aug 2006	Innovator	Single agent	**Benazepril**	Cibace® 10mg	8	57.14	168.48	0.20	1 347.86
				Cibace® 5mg	6	42.86	141.46	0.00	848.76
				Total	**14**	**100.00**	**156.90**	**13.88**	**2 196.62**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	56	100.00	285.45	35.47	15 985.30
				Total	**56**	**100.00**	**285.45**	**35.47**	**15 985.30**

Table B1 (continued): Cost and prevalence of Benazepril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Innovator	Single agent	**Benazepril**	Cibace® 10mg	11	78.57	172.76	51.17	1 900.36
				Cibace® 5mg	3	21.43	141.47	0.01	424.40
				Total	**14**	**100.00**	**166.05**	**46.81**	**2 324.76**
	Innovator	Combination	**Benazepril/HCTZ**	Cibardex® 10/12.5mg	50	100.00	282.08	33.86	14 104.21
				Total	**50**	**100.00**	**282.08**	**33.86**	**14 104.21**

Table B2: Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Captopril**	Capoten® 25mg	875	46.49	195.98	100.98	171 485.32
				Capoten® 50mg	682	36.24	369.95	129.00	252 304.89
				Capoten® HS 12.5mg	325	17.27	142.41	91.95	46 284.81
				Total	**1882**	**100.00**	**249.77**	**144.17**	**470 075.02**
	Generic	Single agent	**Captopril**	Capace® 25 mg	2108	23.31	89.22	45.62	188 068.56
				Captomax® 25mg	2033	22.48	69.81	36.97	141 918.59
				Adco-Captopril® 25mg	955	10.56	73.84	31.86	70 514.70
				Captomax® 50mg	886	9.80	142.83	55.47	126 543.65
				Sandoz-Captopril® 25mg	599	6.62	74.69	31.12	44 740.83
				Zapto® 25mg	555	6.14	76.92	28.07	42 688.97
				CaptoHexal® 12.5mg	489	5.41	65.45	30.91	32 006.26
				Adco-Captopril® 50mg	418	4.62	141.26	44.89	59 047.00
				Captohexal® 25mg	239	2.64	84.47	38.51	20 187.26
				Zapto® 50mg	214	2.37	152.13	52.15	32 555.88
				Sandoz-Captopril® 50mg	198	2.19	167.23	46.13	33 111.33
				Captohexal® 50mg	166	1.84	130.90	51.42	21 729.20
				Cardiace® 25mg	49	0.54	91.05	26.25	4 461.51
				Captopril-Acet® 25mg	46	0.51	86.42	14.43	3 975.12
				Captopril-Acet® 12.5mg	19	0.21	63.72	14.90	1 210.74
				Captopril-Acet® 50mg	19	0.21	198.68	50.45	3 774.99
				Cardiace® 50mg	15	0.17	74.61	21.22	1 119.11
				Apo-Captopril® 25mg	14	0.15	76.90	31.24	1 076.65
				Merck-Captopril® 25mg	14	0.15	63.46	32.45	888.49
				Cardiace® 12.5mg	6	0.07	66.10	18.02	396.62
				Apo-Captopril® 50mg	1	0.01	143.48	0.00	143.48
				Total	**9043**	**100.00**	**91.80**	**50.21**	**830 158.94**

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	477.00	100.00	247.15	75.18	117 891.73
				Total	**477.00**	**100.00**	**247.15**	**75.18**	**117 891.73**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	1070	49.77	165.91	51.55	177 519.32
				Captoretic® 50/25mg	959	44.60	141.67	33.44	135 857.11
				Captoretic® HS	121	5.63	107.87	29.61	13 052.52
				Total	**2150**	**100.00**	**151.83**	**46.08**	**326 428.95**
Year 2004	Innovator	Single agent	**Captopril**	Capoten® 25mg	225	54.09	140.21	103.44	31 547.61
				Capoten® 50mg	126	30.29	213.78	150.59	26 936.40
				Capoten® HS 12.5mg	65	15.63	61.26	47.61	3 981.96
				Total	**416**	**100.01**	**150.16**	**124.40**	**62 465.97**
	Generic	Single agent	**Captopril**	Capace® 25 mg	982	15.14	66.48	37.41	65 287.76
				Captomax® 25mg	873	13.46	53.45	30.64	46 659.09
				Adco-Captopril® 25mg	830	12.79	41.29	33.52	34 271.71
				Sandoz-Captopril® 25mg	774	11.39	32.76	25.64	25 352.46
				CaptoHexal® 25mg	718	11.07	41.02	28.06	29 454.05
				Captomax® 50mg	450	6.94	110.40	51.77	49 681.57
				CaptoHexal® 12.5mg	432	6.66	40.07	23.13	17 310.78
				Adco-Captopril® 50mg	364	5.61	79.16	51.10	28 814.60
				Sandoz-Captopril® 50mg	306	4.72	68.71	47.36	21 025.04
				CaptoHexal® 50mg	235	3.62	69.22	45.97	16 267.42
				Zapto® 25mg	200	3.08	42.23	22.87	8 446.04
				Merck-Captopril® 25mg	162	2.50	27.22	26.63	4 409.98
				Zapto® 50mg	90	1.39	113.77	65.06	10 238.97
				Merck-Captopril® 50mg	64	0.99	33.24	39.06	2 127.23
				Captopril-Acet® 25mg	3	0.05	49.80	19.71	149.39
				Cardiace® 25mg	3	0.05	95.58	41.42	286.75
				Captopril-Acet® 50mg	1	0.02	128.78	0.00	128.78
				Total	**6487**	**99.48**	**55.48**	**42.23**	**359 911.62**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2004	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	285	100.00	258.43	118.30	73 653.14
				Total	**285**	**100.00**	**258.43**	**118.30**	**73 653.14**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	952	49.07	83.62	37.90	79 605.07
				Zapto-Co® 50/25mg	747	38.51	104.45	43.47	78 021.94
				Captoretic® 25/12.5mg	241	12.42	67.95	30.91	16 376.73
				Total	**1940**	**100.00**	**89.69**	**41.36**	**174 003.74**
Year 2005	Innovator	Single agent	**Captopril**	Capoten® 25mg	86	67.72	124.20	131.09	10 680.85
				Capoten® 50mg	31	24.41	145.34	89.20	4 505.53
				Capoten® HS 12.5mg	10	7.87	33.91	36.28	339.08
				Total	**127**	**100.00**	**122.25**	**119.72**	**15 525.46**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	327	15.84	19.06	9.53	6 231.15
				Sandoz-Captopril® 25mg	307	14.87	23.06	11.65	7 080.21
				Adco-Captopril® 50mg	237	11.48	41.07	15.49	9 734.26
				CaptoHexal® 25mg	227	11.00	23.78	9.57	5 397.55
				Capace® 25mg	169	8.19	45.41	36.07	7 675.09
				Sandoz-Captopril® 50mg	157	7.61	46.83	16.42	7 352.71
				Captomax® 25mg	135	6.54	33.98	29.74	4 587.90
				Zapto® 25mg	108	5.23	20.33	8.85	2 195.52
				CaptoHexal® 50mg	100	4.84	36.00	12.82	3 599.98
				CaptoHexal® 12.5mg	77	3.73	19.92	11.53	1 533.76
				Captomax® 50mg	76	3.68	50.29	24.36	3 822.30
				Merck-Captopril® 25mg	60	2.91	11.88	4.97	712.53
				Zapto® 50mg	56	2.71	49.95	19.06	2 797.39
				Merck-Captopril® 50mg	19	0.92	20.56	6.98	390.55
				Aceten® 25mg	9	0.44	6.07	3.22	54.63
				Total	**2064**	**99.99**	**30.60**	**20.99**	**63 165.53**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2005	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	283	100.00	241.26	111.43	68 275.40
				Total	**283**	**100.00**	**241.26**	**111.43**	**68 275.40**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	580	52.25	69.25	24.04	40 164.81
				Zapto-Co® 50/25mg	442	39.82	78.36	21.04	34 634.71
				Captoretic® 25/12.5mg	88	7.93	50.66	15.08	4 457.77
				Total	**1110**	**100.00**	**71.40**	**23.48**	**79 257.29**
Year 2006	Innovator	Single agent	**Captopril**	Capoten® 25mg	18	75.00	193.06	155.73	3 475.00
				Capoten® HS 12.5mg	6	25.00	31.31	30.51	187.84
				Total	**24**	**100.00**	**152.62**	**152.46**	**3 662.84**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	87	23.32	18.28	10.56	1 589.93
				CaptoHexal® 25mg	56	15.01	22.53	6.57	1 261.53
				Adco-Captopril® 50mg	50	13.4	41.41	13.26	2 070.49
				Sandoz-Captopril® 50mg	43	11.53	47.35	11.35	2 036.02
				Zapto® 50mg	34	9.12	56.88	14.93	1 934.08
				Sandoz Captopril® 25mg	23	6.17	14.02	10.06	322.51
				CaptoHexal® 12.5mg	21	5.63	29.72	9.90	624.10
				Zapto® 25mg	19	5.09	10.18	4.14	193.50
				Capace® 25mg	15	4.02	55.35	16.93	830.31
				CaptoHexal® 50mg	13	3.49	35.47	17.18	461.12
				Merck-Captopril® 25mg	8	2.14	8.39	4.10	67.15
				Captomax® 25mg	3	0.8	27.68	31.41	83.03
				Merck-Captopril® 50mg	1	0.27	16.33	0.00	16.33
				Total	**373**	**100.00**	**30.80**	**18.96**	**11 490.10**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	177	100.00	273.15	141.98	48 347.69
				Total	**177**	**100.00**	**273.15**	**141.98**	**48 347.69**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	292	68.07	82.07	18.08	23 963.62
				Captoretic® 50/25mg	113	26.34	85.36	32.50	9 645.70
				Captoretic® 25/12.5mg	24	5.59	53.57	2.33	1 285.63
				Total	**429**	**100.00**	**81.34**	**23.38**	**34 894.95**

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Single agent	**Captopril**	Capoten® 25mg	80	58.82	154.76	98.49	12 381.05
				Capoten® 50mg	34	25.00	228.67	176.34	7 774.76
				Capoten® HS 12.5mg	22	16.18	75.00	38.64	1 649.91
				Total	**136**	**100.00**	**160.34**	**126.06**	**21 805.72**
	Generic	Single agent	**Captopril**	Capace® 25 mg	382	20.82	86.60	36.64	33 082.19
				Captomax® 25mg	327	17.82	62.44	34.30	20 416.93
				Adco-Captopril® 25mg	198	10.79	77.78	33.60	15 400.03
				CaptoHexal® 25mg	167	9.10	72.35	29.48	12 082.79
				Captomax® 50mg	161	8.77	135.71	56.39	21 848.91
				Sandoz-Captopril® 25mg	140	7.63	73.12	27.86	10 236.39
				CaptoHexal® 12.5mg	138	7.52	56.14	23.29	7 747.60
				Adco-Captopril® 50mg	114	6.21	125.36	39.44	14 290.82
				Sandoz-Captopril® 50mg	61	3.32	142.92	46.60	8 718.03
				Zapto® 25mg	52	2.83	61.85	21.33	3 216.12
				Captohexal® 50mg	36	1.96	133.50	49.48	4 806.13
				Zapto® 50mg	26	1.42	153.24	45.11	3 984.26
				Merck-Captopril® 25mg	25	1.36	69.85	16.73	1 746.27
				Merck-Captopril® 50mg	5	0.27	137.55	11.46	687.75
				Cardiace® 25mg	2	0.11	71.67	0.00	143.34
				Captopril-Acet® 50mg	1	0.05	69.95	0.00	69.95
				Total	**1835**	**99.98**	**86.36**	**45.51**	**158 477.51**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	97	100.00	264.53	108.30	25 659.84
				Total	**97**	**100.00**	**264.53**	**108.30**	**25 659.84**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	204	45.33	130.81	40.68	26 685.54
				Captoretic® 50/12.5mg	176	39.11	122.24	34.80	21 513.54
				Captoretic® 25/12.5mg	70	15.56	94.33	26.49	6 602.89
				Total	**450**	**100.00**	**121.78**	**38.51**	**54 801.97**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2004	Innovator	Single agent	**Captopril**	Capoten® 25mg	79	54.48	156.95	98.36	12 398.67
				Capoten® 50mg	42	28.97	245.86	158.24	10 326.30
				Capoten® HS 12.5mg	24	16.55	67.57	62.19	1 621.76
				Total	**145**	**100.00**	**167.91**	**128.47**	**24 346.73**
	Generic	Single agent	**Captopril**	Capace® 25 mg	328	15.80	59.98	33.44	19 674.01
				Captomax® 25mg	291	14.02	53.41	27.68	15 541.58
				Adco-Captopril® 25mg	249	11.99	45.93	29.60	11 437.39
				Sandoz-Captopril® 25mg	230	11.08	27.78	18.27	6 389.78
				CaptoHexal® 25mg	210	10.12	40.27	27.23	8 456.54
				Captomax® 50mg	167	8.04	107.38	43.79	17 932.70
				CaptoHexal® 12.5mg	141	6.79	40.06	21.25	5 648.21
				Adco-Captopril® 50mg	100	4.82	88.61	48.04	8 861.06
				Sandoz-Captopril® 50mg	92	4.43	63.08	34.18	5 803.31
				Captohexal® 50mg	82	3.95	74.51	45.07	6 110.07
				Zapto® 25mg	67	3.23	44.04	21.28	2 951.00
				Merck-Captopril® 25mg	58	2.79	30.01	26.58	1 740.35
				Zapto® 50mg	30	1.45	135.38	74.96	4 061.52
				Merck-Captopril® 50mg	28	1.35	32.09	34.96	898.45
				Captopril-Acet® 25mg	1	0.05	30.57	0.00	30.57
				Captopril-Acet® 50mg	1	0.05	128.78	0.00	128.78
				Cardiace® 25mg	1	0.05	143.41	0.00	143.41
				Total	**2076**	**100.01**	**55.78**	**40.09**	**115 808.73**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	141	100.00	262.64	132.78	37 032.41
				Total	**141**	**100.00**	**262.64**	**132.78**	**37 032.41**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	303	46.76	88.76	36.98	26 893.39
				Zapto-Co® 50/25mg	269	41.51	111.32	34.76	29 946.24
				Captoretic® 25/12.5mg	76	11.73	67.07	31.64	5 097.05
				Total	**648**	**100.00**	**95.58**	**38.41**	**61 936.68**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Innovator	Single agent	**Captopril**	Capoten® 25mg	66	48.89	102.54	106.93	6 767.89
				Capoten® 50mg	50	37.04	176.71	116.28	8 835.34
				Capoten® HS 12.5mg	19	14.07	37.38	22.12	710.29
				Total	**135**	**100.00**	**120.84**	**113.46**	**16 313.52**
	Generic	Single agent	**Captopril**	Sandoz-Captopril® 25mg	404	15.68	21.60	9.94	8 726.29
				Adco-Captopril® 25mg	383	14.87	19.41	10.14	7 434.29
				CaptoHexal® 25mg	341	13.24	26.14	8.73	8 914.72
				Capace® 25mg	272	10.56	46.07	28.12	12 531.56
				Captomax® 25mg	255	9.90	41.96	24.52	10 700.58
				CaptoHexal® 12.5mg	153	5.94	25.59	12.92	3 914.97
				Sandoz-Captopril® 50mg	153	5.94	42.51	12.84	6 503.70
				Adco-Captopril® 50mg	150	5.82	37.75	15.18	5 662.72
				Captomax® 50mg	122	4.74	81.15	37.17	9 899.96
				CaptoHexal® 50mg	117	4.54	45.74	15.73	5 351.22
				Zapto® 25mg	81	3.14	28.13	13.56	2 278.92
				Merck-Captopril® 25mg	79	3.07	11.69	5.34	923.36
				Zapto® 50mg	34	1.32	64.51	27.96	2 193.19
				Merck-Captopril® 50mg	31	1.20	17.45	3.85	541.03
				Captopril-Acet® 25mg	1	0.04	48.87	0.00	48.87
				Total	**2576**	**100.00**	**33.24**	**23.39**	**85 625.38**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	47	100.00	233.21	86.52	10 960.89
				Total	**47**	**100.00**	**223.21**	**86.52**	**10 960.89**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	473	56.18	65.96	26.17	31 198.14
				Zapto-Co® 50/25mg	274	32.54	78.07	38.51	21 390.16
				Captoretic® 25/12.5mg	95	11.28	49.23	15.91	4 676.79
				Total	**842**	**100.00**	**68.01**	**31.13**	**57 265.09**

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Single agent	**Captopril**	Capoten® 25mg	34	61.82	111.33	132.84	3 785.18
				Capoten® 50mg	17	30.91	148.04	104.69	2 516.71
				Capoten® HS 12.5mg	4	7.27	22.73	13.19	90.93
				Total	**55**	**100.00**	**116.23**	**122.56**	**6 392.82**
	Generic	Single agent	**Captopril**	Sandoz-Captopril® 25mg	116	16.67	23.81	13.53	2 762.03
				Adco-Captopril® 25mg	106	15.23	19.75	8.92	2 093.42
				CaptoHexal® 25mg	80	11.49	23.67	9.76	1 893.87
				Adco-Captopril® 50mg	74	10.63	41.47	16.60	3 068.95
				Captomax® 25mg	67	9.63	41.32	30.18	2 768.37
				Capace®	61	8.76	40.90	26.98	2 494.88
				Sandoz-Captopril® 50mg	57	8.19	41.96	18.55	2 391.66
				Captomax® 50mg	34	4.89	55.43	30.70	1 884.65
				CaptoHexal® 50mg	26	3.74	37.27	13.15	969.01
				Zapto® 25mg	26	3.74	20.32	8.04	528.34
				CaptoHexal® 12.5mg	18	2.59	16.83	9.14	302.91
				Merck-Captopril® 25mg	15	2.16	10.57	5.13	158.51
				Zapto® 50mg	12	1.72	56.76	16.47	681.13
				Merck-Captopril® 50mg	3	0.43	26.63	1.37	79.89
				Aceten®	1	0.14	3.09	0.00	3.09
				Total	**696**	**100.01**	**31.73**	**21.33**	**22 080.71**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	69	100.00	221.25	74.40	15 266.54
				Total	**69**	**100.00**	**221.25**	**74.40**	**15 266.54**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	234	58.35	69.75	24.57	16 320.45
				Zapto-Co® 50/25mg	138	34.41	75.70	22.61	10 447.18
				Captoretic® 25/12.5mg	29	7.23	51.24	16.35	1 485.96
				Total	**401**	**99.99**	**70.46**	**24.12**	**28 253.59**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2005	Innovator	Single agent	**Captopril**	Capoten® 50mg	9	18.00	129.71	44.78	1 167.43
				Capoten® HS 12.5mg	5	10.00	46.42	49.30	232.10
				Total	**50**	**100.00**	**130.76**	**120.59**	**6 538.06**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	129	17.09	18.08	9.60	2 331.84
				Sandoz-Captopril® 25mg	90	11.92	23.65	12.61	2 128.84
				CaptoHexal® 25mg	84	11.13	22.85	9.57	1 919.14
				Adco-Captopril® 50mg	83	10.99	41.97	15.91	3 483.71
				Capace®	70	9.27	43.94	35.20	3 075.74
				Sandoz-Captopril® 50mg	56	7.42	47.87	14.09	2 680.52
				Captomax® 25mg	49	6.49	28.47	31.30	1 394.97
				CaptoHexal® 50mg	43	5.70	35.46	11.83	1 524.64
				Zapto® 25mg	34	4.50	21.31	8.58	724.54
				CaptoHexal® 12.5mg	33	4.37	19.11	10.27	630.55
				Captomax® 50mg	26	3.44	47.06	19.16	1 223.65
				Merck-Captopril® 25mg	23	3.05	11.65	6.23	268.04
				Zapto® 50mg	21	2.78	49.03	19.80	1 029.60
				Merck-Captopril® 50mg	8	1.06	20.58	6.23	164.67
				Aceten®	6	0.79	7.56	2.93	45.38
				Total	**755**	**100.00**	**29.97**	**20.98**	**22 625.83**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	109	100.00	239.91	98.20	26 150.35
				Total	**109**	**100.00**	**239.91**	**98.20**	**26 150.35**
	Generic	Combination	**Captopril/HCTZ**	Captoretic® 50/25mg	214	53.10	69.12	22.05	14 792.28
				Zapto-Co® 50/25mg	149	36.97	79.21	21.37	11 802.76
				Captoretic® 25/12.5mg	40	9.93	50.35	15.06	2 014.04
				Total	**403**	**100.00**	**70.99**	**22.74**	**28 609.08**

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Single agent	**Captopril**	Capoten® 50mg	5	22.72	164.28	103.86	821.39
				Capoten® HS 12.5mg	1	4.55	16.05	0.00	16.05
				Total	**6**	**99.99**	**117.94**	**114.70**	**837.44**
	Generic	Single agent	**Captopril**	Sandoz-Captopril® 25mg	101	16.48	21.68	7.75	2 189.34
				Adco-Captopril® 25mg	92	15.01	19.63	10.08	1 805.89
				Adco-Captopril® 50mg	80	13.05	39.77	14.02	3 181.60
				CaptoHexal® 25mg	63	10.28	25.15	9.30	1 584.54
				Zapto® 25mg	48	7.83	19.64	9.54	942.64
				Sandoz-Captopril® 50mg	44	7.18	51.83	14.77	2 280.53
				Capace®	38	6.20	55.38	47.72	2 104.47
				CaptoHexal® 50mg	31	5.06	35.69	14.16	1 106.33
				CaptoHexal® 12.5mg	26	4.24	23.09	13.93	600.30
				Zapto® 50mg	23	3.75	47.25	19.57	1 086.66
				Merck-Captopril® 25mg	22	3.59	13.00	2.94	285.98
				Captomax® 25mg	19	3.10	22.35	14.39	424.56
				Captomax® 50mg	16	2.61	44.63	13.01	714.00
				Merck-Captopril® 50mg	8	1.31	18.25	8.01	145.99
				Aceten®	2	0.33	3.08	0.00	6.16
				Total	**613**	**100.02**	**30.11**	**20.59**	**18 458.99**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	105	100.00	255.80	139.84	26 858.51
				Total	**105**	**100.00**	**255.80**	**139.84**	**26 858.51**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	155	50.65	79.90	19.09	12 384.77
				Captoretic® 50/25mg	132	43.14	68.58	26.23	9 052.08
				Captoretic® 25/12.5mg	19	6.21	50.41	13.84	957.77
				Total	**306**	**100.00**	**73.19**	**23.57**	**22 394.62**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan-Apr 2006	Innovator	Single agent	**Captopril**	Capoten® 25mg	8	72.73	134.24	122.02	1 073.93
				Capoten® HS 12.5mg	3	27.27	11.47	7.93	34.41
				Total	**11**	**100.00**	**100.76**	**117.15**	**1 108.34**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	31	23.48	18.24	13.55	565.48
				CaptoHexa® 25mg	23	17.42	22.07	7.05	507.66
				Adco-Captopril® 50mg	16	12.12	44.64	13.22	714.18
				Sandoz-Captopril® 50mg	14	10.61	49.24	11.72	689.31
				Zapto® 50mg	12	9.09	55.75	14.81	669.53
				Zapto® 25mg	8	6.06	9.05	1.25	72.36
				Capace®	7	5.30	44.71	20.51	312.95
				CaptoHexal® 12.5mg	6	4.55	35.24	8.86	211.44
				Sandoz-Captopril® 25mg	6	4.55	11.74	12.60	70.42
				CaptoHexal® 50mg	5	3.79	41.37	17.63	206.84
				Merck-Captopril® 50mg	3	2.27	7.28	2.05	21.85
				Captomax® 25mg	1	0.76	63.95	0.00	63.95
				Total	**132**	**100.00**	**31.11**	**19.75**	**4 105.97**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	60	100.00	238.88	90.20	14 332.82
				Total	**60**	**100.00**	**238.88**	**90.20**	**14 332.82**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	104	66.67	82.49	20.49	8 578.96
				Captoretic® 50/25mg	41	26.28	87.15	33.31	3 573.00
				Captoretic® 25/12.5mg	11	7.05	53.98	0.82	593.81
				Total	**156**	**100.00**	**81.70**	**25.06**	**12 745.77**

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May-Aug 2006	Innovator	Single agent	**Captopril**	Capoten® 25mg	7	70.00	250.82	183.94	1 755.72
				Capoten® HS 12.5mg	3	30.00	51.14	32.91	153.43
				Total	**10**	**100.00**	**190.92**	**179.16**	**1 909.15**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	23	19.66	19.91	8.07	457.83
				Sandoz-Captopril® 50mg	18	15.38	47.82	12.60	860.70
				CaptoHexal® 25mg	17	14.53	23.62	6.51	401.59
				Adco-Captopril® 50mg	15	12.82	40.54	12.73	608.04
				Zapto® 50mg	13	11.11	54.44	14.94	707.74
				CaptoHexal® 12.5mg	8	6.84	24.08	11.05	192.66
				Sandoz-Captopril® 25mg	8	6.84	14.26	9.88	114.10
				Zapto® 25mg	5	4.27	12.13	7.24	60.66
				Capace®	4	3.42	64.67	0.00	258.68
				CaptoHexal® 50mg	3	2.56	49.19	3.09	147.56
				Captomax® 25mg	1	0.85	9.54	0.00	9.54
				Merck-Captopril® 25mg	1	0.85	1.88	0.00	1.88
				Merck-Captopril® 50mg	1	0.85	16.33	0.00	16.33
				Total	**117**	**99.98**	**32.80**	**18.56**	**3 837.31**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	69	100.00	263.22	154.44	18 162.32
				Total	**69**	**100.00**	**263.22**	**154.44**	**18 162.32**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	97	69.29	79.07	21.53	7 670.10
				Captoretic® 50/25mg	38	27.14	82.77	31.49	3 145.09
				Captoretic® 25/12.5mg	5	3.57	51.85	4.97	259.24
				Total	**140**	**100.00**	**79.10**	**24.81**	**11 074.43**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B2 (continued): Cost and prevalence of Captopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Innovator	Single agent	**Captopril**	Capoten® 25mg	3	100.00	215.12	162.09	645.35
				Total	**3**	**100.00**	**215.12**	**162.09**	**645.35**
	Generic	Single agent	**Captopril**	Adco-Captopril® 25mg	33	26.61	17.17	8.93	566.62
				Adco-Captopril® 50mg	19	15.32	39.38	13.89	748.27
				CaptoHexal® 25mg	16	12.90	22.02	6.19	352.28
				Sandoz-Captopril® 50mg	11	8.87	44.18	8.72	486.01
				Sandoz-Captopril® 25mg	9	7.26	15.33	9.37	137.99
				Zapto® 50mg	9	7.26	61.87	15.60	556.81
				CaptoHexal® 12.5mg	7	5.65	31.43	6.53	220.00
				Zapto® 25mg	6	4.84	10.08	3.41	60.48
				CaptoHexal® 50mg	5	4.03	21.34	11.66	106.72
				Capace®	4	3.23	64.67	0.00	258.68
				Merck-Captopril® 25mg	4	3.23	10.86	3.59	43.42
				Captomax® 25mg	1	0.81	9.54	0.00	9.54
				Total	**124**	**100.01**	**28.60**	**18.38**	**3 546.82**
	Innovator	Combination	**Captopril/HCTZ**	Capozide® 50/25mg	48	100.00	330.26	160.60	15 852.55
				Total	**48**	**100.00**	**330.26**	**160.60**	**15 852.55**
	Generic	Combination	**Captopril/HCTZ**	Zapto-Co® 50/25mg	91	68.42	84.78	8.01	7 714.56
				Captoretic® 50/25mg	34	25.56	86.11	33.41	2 927.61
				Captoretic® 25/12.5mg	8	6.02	54.07	0.00	432.58
				Total	**133**	**100.00**	**83.27**	**19.44**	**11 074.75**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B3: Cost and prevalence of Cilazapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	954	60.15	144.72	37.37	138 066.45
				Inhibace® 5mg	632	39.85	226.94	40.63	143 429.03
				Total	**1586**	**100.00**	**177.49**	**55.84**	**281 495.48**
	Innovator	combination	**Cilazapril/HCTZ**	Inhibace® Plus	1225	100.00	231.10	42.97	283 101.44
				Total	**1225**	**100.00**	**231.10**	**42.97**	**283 101.44**
Year 2004	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	671	54.29	150.70	35.41	101 119.34
				Inhibace® 5mg	565	45.71	196.78	64.24	111 178.24
				Total	**1236**	**100.00**	**171.76**	**55.61**	**212 297.58**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	923	100.00	198.18	62.03	182 923.15
				Total	**923**	**100.00**	**198.18**	**62.03**	**182 923.15**
Year 2005	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	154	50.83	156.02	48.71	24 026.62
				Inhibace® 5mg	149	49.17	148.79	9.31	22 169.41
				Total	**303**	**100.00**	**152.46**	**35.46**	**46 196.03**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	287	100.00	152.89	22.27	43 879.46
				Total	**287**	**100.00**	**152.89**	**22.27**	**43 879.46**
Year 2006	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	30	68.18	207.24	76.38	6 217.28
				Inhibace® 5mg	14	31.82	171.19	2.34	2 396.71
				Total	**44**	**100.00**	**195.77**	**65.00**	**8 613.99**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	48	100.00	154.51	31.57	7 416.67
				Total	**48**	**100.00**	**154.51**	**31.57**	**7 416.67**

Table B3 (continued): Cost and prevalence of Cilazapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	233	57.39	162.41	31.70	37 840.78
				Inhibace® 5mg	173	42.61	263.06	49.05	45 510.06
				Total	**406**	**100.00**	**205.30**	**63.89**	**83 350.84**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	287	100.00	261.62	49.12	75 083.56
				Total	**287**	**100.00**	**261.62**	**49.12**	**75 083.56**
May - Aug 2004	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	212	52.87	152.52	37.26	32 333.23
				Inhibace® 5mg	189	47.13	189.66	53.63	35 846.44
				Total	**401**	**100.00**	**170.02**	**49.28**	**68 179.67**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	276	100.00	193.96	49.50	53 531.63
				Total	**276**	**100.00**	**193.96**	**49.50**	**53 531.63**
Sep - Dec 2004	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	226	52.68	136.93	32.57	30 945.33
				Inhibace® 5mg	203	47.32	146.91	22.07	29 821.74
				Total	**429**	**100.00**	**141.65**	**28.50**	**60 767.07**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	360	100.00	150.86	24.61	54 307.96
				Total	**360**	**100.00**	**150.86**	**24.61**	**54 307.96**

Table B3 (continued): Cost and prevalence of Cilazapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Single	**Cilazapril**	Inhibace® 5mg	54	50.94	147.56	10.99	7 968.48
				Inhibace® 2.5mg	52	49.06	147.70	40.48	7 680.57
				Total	**106**	**100.00**	**147.63**	**29.27**	**15 649.05**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	94	100.00	153.47	26.19	14 425.98
				Total	**94**	**100.00**	**153.47**	**26.19**	**14 425.98**
May - Aug 2005	Innovator	Single	**Cilazapril**	Inhibace® 5mg	55	51.40	148.62	7.65	8 174.00
				Inhibace® 2.5mg	52	48.60	159.99	54.36	8 319.31
				Total	**107**	**100.00**	**154.14**	**38.52**	**16 493.31**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	95	100.00	153.21	22.27	14 554.58
				Total	**95**	**100.00**	**153.21**	**22.27**	**14 554.58**
Sep - Dec 2005	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	50	55.56	160.53	50.16	8 026.74
				Inhibace® 5mg	40	44.44	150.67	8.83	6026.93
				Total	**90**	**100.00**	**156.15**	**38.00**	**14 053.67**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	98	100.00	152.03	17.96	14 898.90
				Total	**98**	**100.00**	**152.03**	**17.96**	**14 898.90**

Table B3 (continued): Cost and prevalence of Cilazapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2006	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	10	58.82	185.23	67.66	1 852.26
				Inhibace® 5mg	7	41.18	171.75	0.37	1 202.25
				Total	**17**	**100.00**	**179.68**	**51.21**	**3 054.51**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	16	100.00	148.15	34.86	2 370.43
				Total	**16**	**100.00**	**148.15**	**34.86**	**2 370.43**
May - Aug 2006	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	12	70.59	194.50	71.80	2 334.03
				Inhibace® 5mg	5	29.41	171.89	0.00	859.45
				Total	**17**	**100.00**	**187.85**	**60.47**	**3 193.48**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	15	100.00	156.59	31.05	2 348.83
				Total	**15**	**100.00**	**156.59**	**31.05**	**2 348.83**
Sep - Dec 2006	Innovator	Single	**Cilazapril**	Inhibace® 2.5mg	8	80.00	253.87	82.03	2 030.99
				Inhibace® 5mg	2	20.00	167.51	6.20	335.01
				Total	**10**	**100.00**	**236.60**	**81.02**	**2 366.00**
	Innovator	Combination	**Cilazapril/HCTZ**	Inhibace® Plus	17	100.00	158.67	29.68	2 697.41
				Total	**17**	**100.00**	**158.67**	**29.68**	**2 697.41**

Table B4: Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Enalapril**	Renitec® 10mg	4837	37.16	143.77	58.71	695 413.54
				Renitec® 20mg	4802	36.90	236.83	82.65	1 137 265.06
				Renitec® 5mg	2856	21.94	104.18	42.78	297 527.85
				Renitec® 2.5mg	520	4.00	88.33	30.66	45 933.89
				Total	**13015**	**100.00**	**167.20**	**85.75**	**2 176 140.34**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	3448	20.01	110.79	39.06	381 989.73
				HR-Enalapril® 10mg	3418	19.83	118.35	37.68	404 510.96
				Pharmapress® 20mg	3400	19.73	176.50	56.83	600 094.20
				HR-Enalapril® 20mg	2761	16.02	184.11	48.27	508 337.29
				HR-Enalapril® 5mg	1740	10.10	89.98	33.83	156 569.16
				Adco-Enalapril® 10mg	628	3.64	92.15	30.22	57 870.77
				Adco-Enalapril® 20mg	430	2.50	154.49	36.26	66 430.73
				Enap® 20mg	351	2.04	161.28	40.49	56 609.77
				Enap® 10mg	267	1.55	97.69	23.04	26 083.11
				Enap® 5mg	153	0.89	67.24	16.74	10 288.26
				Ciplatec® 10mg	145	0.84	88.06	37.58	12 768.05
				Hypace® 5mg	122	0.71	37.98	22.92	4 633.30
				Alapren® 10mg	117	0.68	96.40	17.53	11 279.37
				HR-Enalapril® 2.5mg	90	0.52	98.94	34.51	8 904.92
				Alapren® 5mg	69	0.40	79.73	21.78	5 501.69
				Alapren® 20mg	47	0.27	163.11	36.90	7 666.05
				Ciplatec® 5mg	47	0.27	48.32	9.57	2 271.05
				Total	**17233**	**100.00**	**134.73**	**56.96**	**2 321 808.41**

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	8295	100.00	236.87	64.87	1 964 838.06
				Total	**8295**	**100.00**	**236.87**	**64.87**	**1 964 838.06**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	3589	87.66	179.53	37.29	644 316.77
				Enap-Co®	505	12.34	164.89	19.64	83 270.18
				Total	**4094**	**100.00**	**177.72**	**35.91**	**727 586.95**
Year 2004	Innovator	Single agent	**Enalapril**	Renitec® 20mg	2720	37.62	110.12	37.88	299 530.19
				Renitec® 10mg	2357	32.60	61.10	23.11	144 022.87
				Renitec® 5mg	1836	25.39	44.46	18.81	81 624.92
				Renitec® 2.5mg	317	4.38	60.14	14.27	19 064.92
				Total	**7230**	**99.99**	**75.28**	**39.82**	**544 242.90**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	5586	29.20	47.57	17.59	265 711.35
				Pharmapress® 20mg	5346	27.95	88.94	36.10	475 491.97
				HR-Enalapril® 10mg	1677	8.77	50.81	17.57	85 212.91
				HR-Enalapril® 5mg	1184	6.19	48.41	17.90	57 317.09
				HR-Enalapril® 20mg	1161	6.07	100.64	35.48	116 841.66
				Adco-Enalapril® 10mg	751	3.93	52.09	20.80	39 118.67
				Enap® 10mg	655	3.42	51.61	17.84	33 807.00
				Enap® 5mg	491	2.57	43.99	17.92	21 598.83
				Enap® 20mg	476	2.49	91.29	32.99	43 455.25
				Ciplatec® 10mg	410	2.14	56.01	21.32	22 964.42
				Adco-Enalapril® 20mg	344	1.80	118.00	37.97	40 591.09
				Ciplatec® 5mg	249	1.30	37.08	16.07	9 233.81
				Alapren® 10mg	191	1.00	45.56	13.08	8 702.35
				Alapren® 20mg	178	0.93	92.33	47.56	16 434.36
				HR-Enalapril® 2.5mg	139	0.73	49.06	17.56	6 819.60
				Alapren® 5mg	114	0.60	31.77	11.70	3 621.91
				Ciplatec® 20mg	111	0.58	75.37	20.25	8 366.61
				Hypace®	64	0.33	26.25	6.39	1 680.19
				Total	**19127**	**100.00**	**65.72**	**34.59**	**1 256 969.07**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2004	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	4757	100.00	118.57	33.26	564 051.15
				Total	**4757**	**100.00**	**118.57**	**33.26**	**564 051.15**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	6851	87.32	95.31	33.96	652 970.28
				Enap-Co®	995	12.68	110.41	34.67	109 857.57
				Total	**7846**	**100.00**	**97.23**	**34.42**	**762 827.85**
Year 2005	Innovator	Single agent	**Enalapril**	Renitec® 10mg	1112	39.33	53.69	23.60	59 702.28
				Renitec® 20mg	906	32.05	86.66	30.28	78 513.50
				Renitec® 5mg	727	25.72	36.15	15.38	26 279.08
				Renitec® 2.5mg	82	2.90	56.67	19.41	4 647.03
				Total	**2827**	**100.00**	**59.83**	**31.21**	**169 141.89**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	2908	29.14	42.65	14.64	124 030.18
				Pharmapress® 20mg	2744	27.49	72.42	19.65	198 727.82
				HR-Enalapril® 10mg	725	7.26	42.66	13.86	30 925.74
				HR-Enalapril® 20mg	509	5.10	70.69	23.96	35 980.91
				Enap® 20mg	439	4.40	69.37	14.12	30 454.55
				HR-Enalapril® 5mg	362	3.63	31.05	14.17	11 241.20
				Enap® 10mg	359	3.60	43.46	13.14	15 603.24
				Enap® 5mg	335	3.36	30.51	11.88	10 220.52
				Alapren® 10mg	260	2.60	46.43	15.57	12 071.51
				Ciplatec® 5mg	234	2.34	32.71	17.05	7 655.24
				Alapren® 20mg	210	2.10	66.39	7.74	13 941.66
				Adco-Enalapril® 10mg	202	2.02	43.33	11.40	8 752.82
				Ciplatec® 10mg	189	1.89	44.60	12.56	8 430.06
				Ciplatec® 20mg	179	1.79	71.54	15.07	12 804.88
				Alapren® 5mg	144	1.44	26.03	5.17	3 747.83
				Adco-Enalapril® 20mg	102	1.02	84.75	23.61	8 644.21
				HR-Enalapril® 2.5mg	47	0.47	40.72	11.94	1 913.71
				Hypace® 5mg	33	0.33	19.20	0.90	633.64
				Total	**9981**	**99.98**	**53.68**	**22.94**	**535 779.72**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2005	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	1571	100.00	95.34	45.86	149 782.14
				Total	**1571**	**100.00**	**95.34**	**45.86**	**149 782.14**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	4030	80.10	78.93	11.83	318 070.26
				Enap-Co®	1001	19.90	79.43	14.72	79 506.54
				Total	**5031**	**100.00**	**79.03**	**12.46**	**397 576.80**
Year 2006	Innovator	Single agent	**Enalapril**	Renitec® 20mg	301	44.46	93.77	30.95	28 224.30
				Renitec® 10mg	230	33.97	59.72	28.05	13 735.93
				Renitec® 2.5mg	134	19.79	39.73	15.26	5 323.76
				Renitec® 5mg	12	1.77	92.14	21.60	1 105.67
				Total	**677**	**100.00**	**71.48**	**34.94**	**48 389.66**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	686	24.37	47.99	12.59	32 922.53
				Pharmapress® 20mg	670	23.80	82.14	20.45	55 035.02
				Alapren® 10mg	218	7.74	45.11	11.21	9 833.66
				Alapren® 20mg	188	6.68	68.88	9.46	12 949.48
				Ciplatec® 5mg	166	5.90	36.26	12.84	6 018.77
				Enap® 20mg	158	5.61	75.11	10.18	11 867.10
				Enap® 5mg	132	4.69	30.45	9.20	4 019.05
				Enap® 10mg	123	4.37	44.11	9.33	5 425.27
				Alapren® 5mg	113	4.01	29.74	4.09	3 360.65
				HR-Enalapril® 10mg	102	3.62	46.58	18.23	4 751.15
				Adco-Enalapril® 10mg	74	2.63	51.78	9.86	3 831.92
				Ciplatec® 20mg	52	1.85	87.39	40.76	4 544.33
				Adco-Enalapril® 20mg	50	1.78	92.35	23.68	4 617.32
				Ciplatec® 10mg	35	1.24	42.10	4.66	1 473.58
				HR-Enalapril® 20mg	30	1.07	84.23	27.54	2 526.93
				HR-Enalapril® 5mg	15	0.53	41.97	28.38	629.56
				HR-Enalapril® 2.5mg	2	0.07	44.94	0.00	89.88
				Hypace® 5mg	1	0.04	17.85	0.00	17.85
				Total	**2815**	**100.00**	**58.23**	**24.56**	**163 914.05**

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	384	100.00	112.83	82.21	43 325.26
				Total	**384**	**100.00**	**82.21**	**95.10**	**43 325.26**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	873	64.67	93.69	24.63	81 788.14
				Enap-Co®	477	35.33	89.00	16.00	42 452.31
				Total	**1350**	**100.00**	**92.03**	**22.08**	**124 240.45**
Jan - Apr 2004	Innovator	Single agent	**Enalapril**	Renitec® 20mg	865	37.53	129.00	36.96	111 585.29
				Renitec® 10mg	753	32.67	68.59	23.96	51 652.01
				Renitec® 5mg	565	24.51	54.44	17.78	30 760.39
				Renitec® 2.5mg	122	5.29	64.35	10.53	7 851.15
				Total	**2305**	**100.00**	**87.57**	**42.92**	**201 848.84**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	1492	28.24	62.71	18.03	93 557.05
				Pharmapress® 20mg	1403	26.55	135.61	29.86	190 257.57
				HR-Enalapril® 10mg	559	10.58	63.74	17.49	35 633.05
				HR-Enalapril® 5mg	409	7.74	55.89	16.77	22 860.81
				HR-Enalapril® 20mg	309	5.85	137.96	34.83	42 628.36
				Adco-Enalapril® 10mg	245	4.64	58.86	21.05	14 421.09
				Enap® 10mg	190	3.60	61.82	19.51	11 745.92
				Enap® 5mg	130	2.46	56.52	20.52	7 347.36
				Enap® 20mg	123	2.33	126.01	19.61	15 499.02
				Adco-Enalapril® 20mg	106	2.01	136.01	41.24	14 417.40
				Ciplatec® 10mg	102	1.93	66.06	24.17	6737.87
				Ciplatec® 5mg	49	0.93	51.39	18.55	2 518.27
				HR-Enalapril® 2.5mg	47	0.89	64.46	14.43	3 029.46
				Alapren® 20mg	41	0.78	127.46	61.91	5 225.75
				Alapren® 10mg	34	0.64	60.29	4.49	2 049.92
				Hypace® 5mg	20	0.38	28.17	6.59	563.36
				Alapren® 5mg	13	0.25	48.38	2.59	628.89
				Ciplatec® 20mg	12	0.23	112.17	7.71	1 345.99
				Total	**5284**	**100.03**	**89.04**	**43.43**	**470 467.14**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	1454	100.00	139.55	27.12	202 911.64
				Total	**1454**	**100.00**	**139.55**	**27.12**	**202 911.64**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	1588	85.33	147.81	23.75	234 714.53
				Enap-Co®	273	14.67	141.79	26.29	38 708.24
				Total	**1861**	**100.00**	**146.92**	**24.23**	**273 422.77**
May - Aug 2004	Innovator	Single agent	**Enalapril**	Renitec® 20mg	950	38.90	110.85	40.72	105 305.72
				Renitec® 10mg	797	32.64	63.06	21.92	50 257.88
				Renitec® 5mg	593	24.28	46.75	15.23	27 724.34
				Renitec® 2.5mg	102	4.18	60.41	14.64	6 162.16
				Total	**2442**	**100.00**	**77.58**	**40.12**	**189 450.10**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	1709	28.86	45.77	14.81	78 226.44
				Pharmapress® 20mg	1621	27.38	78.09	23.83	126 589.11
				HR-Enalapril® 10mg	474	8.01	48.04	14.06	22 771.69
				HR-Enalapril® 5mg	407	6.87	49.31	16.55	20 070.67
				HR-Enalapril® 20mg	387	6.54	94.35	26.34	36 512.47
				Adco-Enalapril® 10mg	270	4.56	52.87	22.40	14 274.77
				Enap® 10mg	220	3.72	53.64	16.29	11 801.10
				Enap® 5mg	150	2.53	46.34	13.74	6 951.18
				Enap® 20mg	140	2.36	98.06	24.77	13 727.97
				Adco-Enalapril® 20mg	126	2.13	125.30	35.11	15 787.17
				Ciplatec® 10mg	123	2.08	59.07	19.99	7 265.37
				Ciplatec® 5mg	66	1.11	40.67	12.48	2 684.12
				Alapren® 10mg	60	1.01	47.20	13.63	2 831.94
				Alapren® 20mg	59	1.00	103.19	45.45	6 088.12
				HR-Enalapril® 2.5mg	37	0.62	41.65	13.85	1 541.06
				Ciplatec® 20mg	29	0.49	81.31	18.57	2 357.96
				Alapren® 5mg	28	0.47	42.56	9.82	1 191.65
				Hypace® 5mg	15	0.25	28.02	1.37	420.34
				Total	**5921**	**99.99**	**62.67**	**28.55**	**371 093.13**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2004	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	1634	100.00	119.35	30.88	195 024.06
				Total	**1634**	**100.00**	**119.35**	**30.88**	**195 024.06**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	2135	86.44	85.38	19.89	182 281.94
				Enap-Co®	335	13.56	112.58	34.89	37 712.73
				Total	**2470**	**100.00**	**89.07**	**24.36**	**219 994.67**
Sep-Dec 2004	Innovator	Single agent	**Enalapril**	Renitec® 20mg	905	36.45	91.31	23.94	82 639.18
				Renitec® 10mg	807	32.50	52.18	20.37	42 112.98
				Renitec® 5mg	678	27.31	34.13	17.26	23 140.19
				Renitec® 2.5mg	93	3.75	54.32	16.14	5 051.61
				Total	**2483**	**100.01**	**61.60**	**31.51**	**152 943.96**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	2385	30.11	39.38	12.30	93 927.86
				Pharmapress® 20mg	2322	29.31	68.32	15.57	158 645.29
				HR-Enalapril® 10mg	644	8.13	41.63	12.56	26 808.17
				HR-Enalapril® 20mg	465	5.87	81.08	20.52	37 700.83
				HR-Enalapril® 5mg	368	4.65	39.09	16.34	14 385.61
				Enap® 10mg	245	3.09	41.88	11.84	10 259.98
				Adco-Enalapril® 10mg	236	2.98	44.16	15.32	10 422.81
				Enap® 20mg	213	2.69	66.80	21.95	14 228.26
				Enap® 5mg	211	2.66	34.60	12.94	7 300.29
				Ciplatec® 10mg	185	2.34	48.44	17.46	8961.18
				Ciplatec® 5mg	134	1.69	30.09	12.24	4 031.42
				Adco-Enalapril® 20mg	112	1.41	92.74	21.10	10 386.52
				Alapren® 10mg	97	1.22	39.39	10.03	3 820.49
				Alapren® 20mg	78	0.98	65.65	13.61	5 120.49
				Alapren® 5mg	73	0.92	24.68	5.61	1 801.37
				Ciplatec® 20mg	70	0.88	66.61	13.28	4 662.66
				HR-Enalapril® 2.5mg	55	0.69	40.89	13.06	2 249.08
				Hypace® 5mg	29	0.37	24.02	7.22	696.49
				Total	**7922**	**99.99**	**52.44**	**21.82**	**415 408.80**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep-Dec 2004	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	1669	100.00	99.53	28.87	166 115.45
				Total	**1669**	**100.00**	**99.53**	**28.87**	**166 115.45**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	3128	88.99	75.44	10.44	235 973.81
				Enap-Co®	387	11.01	86.40	16.61	33 436.60
				Total	**3515**	**100.00**	**76.65**	**11.79**	**269 410.41**
Jan - Apr 2005	Innovator	Single agent	**Enalapril**	Renitec® 10mg	382	38.01	52.39	21.01	20 013.29
				Renitec® 20mg	327	32.54	89.78	30.14	29 359.22
				Renitec® 5mg	262	26.07	36.12	14.51	9 462.26
				Renitec® 2.5mg	34	3.38	59.84	17.35	2 034.39
				Total	**1005**	**100.00**	**60.57**	**31.41**	**60 869.16**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	900	29.90	41.14	13.98	37 025.31
				Pharmapress® 20mg	784	26.05	71.13	19.70	55 762.85
				HR-Enalapril® 10mg	235	7.81	41.64	11.42	9 784.41
				HR-Enalapril® 20mg	150	4.98	78.65	29.49	11 797.38
				HR-Enalapril® 5mg	118	3.92	35.58	18.64	4 198.75
				Enap® 5mg	117	3.89	31.38	13.39	3 672.04
				Enap® 20mg	114	3.79	67.86	12.16	7 736.29
				Enap® 10mg	98	3.26	42.11	11.05	4 126.76
				Alapren® 10mg	82	2.72	45.91	16.09	3 764.56
				Adco-Enalapril® 10mg	72	2.39	43.44	13.49	3 127.93
				Ciplatec® 10mg	64	2.13	48.25	15.64	3 088.15
				Ciplatec® 5mg	61	2.03	29.70	18.85	1 811.81
				Ciplatec® 20mg	59	1.96	73.33	14.92	4 326.66
				Alapren® 5mg	56	1.86	24.85	7.07	1 391.73
				Alapren® 20mg	39	1.30	64.82	6.65	2 527.92
				Adco-Enalapril® 20mg	35	1.16	79.76	15.79	2 791.61
				HR-Enalapril® 2.5mg	14	0.47	36.14	4.08	505.95
				Hypace® 5mg	12	0.40	19.09	0.61	229.04
				Total	**3010**	**100.02**	**52.38**	**23.26**	**157 669.15**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	587	100.00	96.78	32.48	56 810.23
				Total	**587**	**100.00**	**96.78**	**32.48**	**56 810.23**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	1219	83.95	77.65	10.93	94 651.58
				Enap-Co®	233	16.05	75.88	12.76	17 679.20
				Total	**1452**	**100.00**	**77.36**	**11.25**	**112 330.78**
May - Aug 2005	Innovator	Single agent	**Enalapril**	Renitec® 10mg	390	38.73	54.54	24.67	21 270.15
				Renitec® 20mg	317	31.48	85.45	29.05	27 089.17
				Renitec® 5mg	270	26.81	36.19	17.45	9 770.55
				Renitec® 2.5mg	30	2.98	57.31	20.15	1 719.21
				Total	**1007**	**100.00**	**59.43**	**31.01**	**59 849.08**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	1077	29.82	43.21	15.49	46 540.60
				Pharmapress® 20mg	986	27.30	71.97	17.50	70 964.11
				HR-Enalapril® 10mg	249	6.89	42.52	14.38	10 587.18
				HR-Enalapril® 20mg	173	4.79	70.57	24.57	12 209.46
				Enap® 20mg	152	4.21	69.76	15.35	10 603.13
				Enap® 10mg	137	3.79	43.69	12.76	5 985.14
				HR-Enalapril® 5mg	115	3.18	29.37	12.04	3 377.63
				Enap® 5mg	113	3.13	31.33	13.04	3 539.97
				Alapren® 10mg	97	2.69	46.45	15.74	4 505.46
				Ciplatec® 5mg	93	2.57	33.12	17.27	3 080.21
				Alapren® 20mg	82	2.27	66.14	7.51	5 423.21
				Adco-Enalapril® 10mg	76	2.10	42.35	8.29	3 218.42
				Ciplatec® 10mg	73	2.02	41.98	9.66	3 064.23
				Ciplatec® 20mg	73	2.02	71.17	17.30	5 195.69
				Alapren® 5mg	49	1.36	25.73	3.36	1 260.79
				Adco-Enalapril® 20mg	40	1.11	88.49	28.75	3 539.66
				HR-Enalapril® 2.5mg	15	0.42	39.54	9.25	593.14
				Hypace® 5mg	12	0.33	19.08	0.55	228.99
				Total	**3612**	**100.00**	**53.69**	**22.58**	**193 917.02**

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2005	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	546	100.00	94.43	29.56	51 560.66
				Total	**546**	**100.00**	**94.43**	**29.56**	**51 560.66**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	1435	77.74	78.93	11.83	113 264.92
				Enap-Co®	411	22.26	80.58	14.23	33 119.32
				Total	**1846**	**100.00**	**79.30**	**12.42**	**146 384.24**
Sep - Dec 2005	Innovator	Single agent	**Enalapril**	Renitec® 10mg	340	41.72	54.17	25.05	18 418.84
				Renitec® 20mg	262	32.15	84.22	31.66	22 065.11
				Renitec® 5mg	195	23.93	36.13	13.39	7 046.27
				Renitec® 2.5mg	18	2.21	49.64	21.09	893.43
				Total	**815**	**100.01**	**59.42**	**31.24**	**48 423.65**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	974	29.00	73.92	21.51	72 000.86
				Pharmapress® 20mg	931	27.72	43.46	14.15	40 464.27
				HR-Enalapril® 10mg	241	7.17	43.79	15.38	10 554.15
				HR-Enalapril® 20mg	186	5.54	64.38	14.93	11 974.07
				Enap® 20mg	173	5.15	70.03	14.19	12 115.13
				HR-Enalapril® 5mg	129	3.84	28.41	9.54	3 664.82
				Enap® 10mg	124	3.69	44.29	14.98	5 491.34
				Enap® 5mg	105	3.13	28.65	8.05	3 008.51
				Alapren® 20mg	89	2.65	67.31	8.32	5 990.53
				Alapren® 10mg	81	2.41	46.93	15.01	3 801.49
				Ciplatec® 5mg	80	2.38	34.54	15.14	2 763.22
				Adco-Enalapril® 10mg	54	1.61	44.56	12.19	2 406.47
				Ciplatec® 10mg	52	1.55	43.80	10.99	2 277.68
				Ciplatec® 20mg	47	1.40	69.84	11.05	3 282.53
				Alapren® 5mg	39	1.16	28.08	2.78	1 095.31
				Adco-Enalapril® 20mg	27	0.80	85.66	23.30	2 312.94
				HR-Enalapril® 2.5mg	18	0.54	45.26	16.19	814.62
				Hypace® 5mg	9	0.27	19.51	1.48	175.61
				Total	**3359**	**100.01**	**54.84**	**22.98**	**184 193.55**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	438	100.00	94.55	71.04	41 411.25
				Total	**438**	**100.00**	**94.55**	**71.04**	**41 411.25**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	1376	79.40	80.05	12.49	110 153.76
				Enap-Co®	357	20.60	80.41	16.07	28 708.02
				Total	**1733**	**100.00**	**80.13**	**13.30**	**138 861.78**
Jan-Apr 2006	Innovator	Single agent	**Enalapril**	Renitec® 20mg	101	43.16	92.39	26.62	9 331.65
				Renitec® 10mg	82	35.04	59.57	27.68	4 884.74
				Renitec® 5mg	47	20.09	42.18	19.60	1 982.32
				Renitec® 2.5mg	4	1.71	76.85	8.53	307.38
				Total	**234**	**100.00**	**70.54**	**32.55**	**16 506.09**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	237	23.84	47.51	12.96	11 260.76
				Pharmapress® 20mg	231	23.24	82.33	20.02	19 018.54
				Alapren® 10mg	89	8.95	47.71	14.86	4 246.23
				Alapren® 20mg	60	6.04	68.20	7.21	4 091.79
				Enap® 20mg	58	5.84	74.66	3.41	4 330.38
				Ciplatec® 5mg	46	4.63	38.35	16.40	1 764.10
				Alapren® 5mg	42	4.23	29.68	4.05	1 246.48
				HR-Enalapril® 10mg	40	4.02	47.35	18.86	1 893.87
				Adco-Enalapril® 10mg	39	3.92	49.10	7.99	1 915.07
				Enap® 5mg	39	3.92	31.56	9.97	1 230.71
				Enap® 10mg	37	3.72	41.81	11.43	1 547.05
				Adco-Enalapril® 20mg	20	2.01	95.93	24.59	1 918.60
				Ciplatec® 20mg	20	2.01	89.67	45.94	1 793.36
				HR-Enalapril® 20mg	15	1.51	76.82	15.15	1 152.37
				Ciplatec® 10mg	14	1.41	44.02	3.18	616.29
				HR-Enalapril® 2.5mg	7	0.70	47.59	37.39	333.10
				Total	**994**	**99.99**	**58.71**	**24.65**	**58 358.70**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan-Apr 2006	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	126	100.00	115.01	95.54	14 491.11
				Total	**126**	**100.00**	**115.01**	**95.54**	**14 491.11**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	289	64.94	88.21	10.87	25 492.79
				Enap-Co®	156	35.06	88.27	16.81	13 770.22
May-Aug 2006	Innovator	Single agent	**Enalapril**	Renitec® 20mg	104	45.41	92.78	30.35	9 649.40
				Renitec® 10mg	75	32.75	57.77	27.22	4 332.69
				Renitec® 5mg	47	20.52	38.61	13.25	1 814.70
				Renitec® 2.5mg	3	1.31	92.50	19.73	277.51
				Total	**229**	**99.99**	**70.19**	**34.51**	**16 074.30**
	Generic	Single agent	**Enalapril**	Pharmapress® 10mg	246	26.11	48.36	12.81	11 896.12
				Pharmapress® 20mg	230	24.42	82.70	20.99	19 021.16
				Alapren® 20mg	67	7.11	67.95	8.92	4 552.63
				Alapren® 10mg	66	7.01	44.38	8.33	2 928.84
				Ciplatec® 5mg	57	6.05	37.06	12.31	2 112.62
				Enap® 20mg	48	5.10	75.52	2.78	3 624.78
				Enap® 5mg	45	4.78	29.31	5.55	1 319.04
				Alapren® 5mg	35	3.72	29.29	2.57	1 025.32
				Enap® 10mg	35	3.72	44.17	3.98	1 544.09
				HR-Enalapril® 10mg	34	3.61	46.65	18.11	1 585.94
				Adco-Enalapril® 10mg	23	2.44	53.81	10.64	1 237.54
				Adco-Enalapril® 20mg	17	1.80	91.35	24.49	1 552.92
				Ciplatec® 20mg	15	1.59	80.69	35.42	1 210.28
				Ciplatec® 10mg	13	1.38	41.22	4.88	535.92
				HR-Enalapril® 20mg	7	0.74	95.29	35.61	667.05
				HR-Enalapril® 5mg	4	0.42	46.81	10.91	187.23
				Total	**942**	**100.00**	**58.39**	**24.18**	**55 001.48**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May-Aug 2006	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	137	100.00	109.33	59.44	14 977.71
				Total	**137**	**100.00**	**109.33**	**59.44**	**14 977.71**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	294	65.19	91.95	21.78	27 032.10
				Enap-Co®	157	34.81	89.71	15.73	14 084.39
				Total	**451**	**100.00**	**91.17**	**19.90**	**41 116.49**
Sep - Dec 2006	Innovator	Single agent	**Enalapril**	Renitec® 20mg	96	44.86	96.28	35.66	9 243.25
				Renitec® 10mg	73	34.11	61.90	29.51	4 518.50
				Renitec® 5mg	40	18.69	38.17	11.09	1 526.74
				Renitec® 2.5mg	5	2.34	104.16	24.90	520.78
				Total	**214**	**100.00**	**73.88**	**37.84**	**15 809.27**
	Generic	Single agent	**Enalapril**	Pharmapress® 20mg	209	23.78	81.32	20.39	16 995.32
				Pharmapress® 10mg	203	23.09	48.11	11.89	9 765.65
				Alapren® 10mg	63	7.17	42.20	5.88	2 658.59
				Ciplatec® 5mg	63	7.17	34.00	9.88	2 142.05
				Alapren® 20mg	61	6.94	70.57	11.66	4 305.06
				Enap® 20mg	52	5.92	75.23	17.28	3 911.94
				Enap® 10mg	51	5.80	45.77	10.05	2 334.13
				Enap® 5mg	48	5.46	30.61	11.15	1 469.30
				Alapren® 5mg	36	4.10	30.25	5.24	1 088.85
				HR-Enalapril® 10mg	28	3.19	45.41	18.07	1 271.34
				Ciplatec® 20mg	17	1.93	90.63	40.40	1 540.69
				Adco-Enalapril® 20mg	13	1.48	88.14	22.13	1 145.80
				Adco-Enalapril® 10mg	12	1.37	56.61	11.81	679.31
				Ciplatec® 10mg	8	0.91	40.17	5.74	321.37
				HR-Enalapril® 20mg	8	0.91	88.44	36.55	707.51
				HR-Enalapril® 5mg	4	0.46	27.31	21.31	109.23
				HR-Enalapril® 2.5mg	2	0.23	44.94	0.00	89.88
				Hypace® 5mg	1	0.11	17.85	0.00	17.85
				Total	**879**	**100.02**	**57.51**	**24.88**	**50 553.87**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B4 (continued): Cost and prevalence of Enalapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Innovator	Combination	**Enalapril/HCTZ**	Co-Renitec®	121	100.00	114.52	89.65	13 856.44
				Total	**121**	**100.00**	**114.52**	**89.65**	**13 856.44**
	Generic	Combination	**Enalapril/HCTZ**	Pharmapress Co®	290	63.88	100.91	33.87	29 263.25
				Enap-Co®	164	36.12	89.01	15.52	14 597.70
				Total	**454**	**100.00**	**96.61**	**29.17**	**43 860.95**

Table B5: Cost and prevalence of Fosinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	1512	64.42	174.86	43.61	264 381.23
				Monopril® 20mg	835	35.58	244.70	42.02	204 326.79
				Total	**2347**	**100.00**	**199.71**	**54.51**	**468 708.02**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	1025	100.00	239.75	40.10	245 742.40
				Total	**1025**	**100.00**	**239.75**	**40.10**	**245 742.40**
Year 2004	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	844	60.85	173.15	42.76	146 142.57
				Monopril® 20mg	543	39.15	247.23	73.50	134 247.72
				Total	**1387**	**100.00**	**202.16**	**67.33**	**280 390.29**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	870	100.00	238.48	51.46	207 481.83
				Total	**870**	**100.00**	**238.48**	**51.46**	**207 481.83**
Year 2005	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	301	62.97	175.62	27.52	52 860.33
				Monopril® 20mg	177	37.03	206.09	40.66	36 478.15
				Total	**478**	**100.00**	**186.90**	**36.10**	**89 338.48**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	210	100.00	230.78	40.19	48 463.01
				Total	**210**	**100.00**	**230.78**	**40.19**	**48 463.01**
Year 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	52	81.25	165.41	35.90	8 601.52
				Monopril® 20mg	12	18.75	205.97	121.12	2 471.69
				Total	**64**	**100.00**	**173.02**	**62.12**	**11 073.21**
	Generic	Single agent	**Fosinopril**	Merck-Fosinopril® 10mg	19	76.00	129.02	4.77	2 451.34
				Merck-Fosinopril® 20mg	6	24.00	177.09	0.00	1 062.54
				Total	**25**	**100.00**	**140.56**	**21.36**	**3 513.88**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	30	100.00	248.12	33.45	7 443.71
				Total	**30**	**100.00**	**248.12**	**33.45**	**7 443.71**

Table B5 (continued): Cost and prevalence of Fosinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	276	60.66	190.20	43.27	52 494.68
				Monopril® 20mg	179	39.34	279.99	79.26	50 118.49
				Total	**455**	**100.00**	**225.52**	**74.33**	**102 613.17**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	264	100.00	259.52	42.58	68 514.41
				Total	**264**	**100.00**	**259.52**	**42.58**	**68 514.41**
May - Aug 2004	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	277	60.88	173.51	39.83	48 061.46
				Monopril® 20mg	178	39.12	253.41	64.40	45 107.16
				Total	**455**	**100.00**	**204.77**	**64.07**	**93 168.62**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	295	100.00	246.75	48.98	72 791.00
				Total	**295**	**100.00**	**246.75**	**48.98**	**72 791.00**
Sep - Dec 2004	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	291	61.01	156.65	38.49	45 586.43
				Monopril® 20mg	186	38.99	209.80	57.71	39 022.07
				Total	**477**	**100.00**	**177.38**	**53.57**	**84 608.50**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	311	100.00	212.79	50.07	66 176.42
				Total	**311**	**100.00**	**212.79**	**50.07**	**66 176.42**
Jan - Apr 2005	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	106	66.25	176.54	34.33	18 713.31
				Monopril® 20mg	54	33.75	208.43	38.90	11 254.98
				Total	**160**	**100.00**	**187.30**	**38.88**	**29 968.29**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	79	100.00	223.34	42.56	17 643.97
				Total	**79**	**100.00**	**223.34**	**42.56**	**17 643.97**
May - Aug 2005	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	109	61.93	175.83	27.50	19 165.76
				Monopril® 20mg	67	38.07	206.90	39.95	13 862.48
				Total	**176**	**100.00**	**187.66**	**36.02**	**33 028.24**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	72	100.00	239.25	41.02	17 226.17
				Total	**72**	**100.00**	**239.25**	**41.02**	**17 226.17**

Table B5 (continued): Cost and prevalence of Fosinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	86	60.56	174.20	15.88	14 981.26
				Monopril® 20mg	56	39.44	202.87	43.59	11 360.69
				Total	**142**	**100.00**	**185.51**	**33.03**	**26 341.95**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	59	100.00	230.39	34.07	13 592.87
				Total	**59**	**100.00**	**230.39**	**34.07**	**13 592.87**
Jan - Apr 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	29	87.88	181.39	26.95	5 260.40
				Monopril® 20mg	4	12.12	290.56	85.75	1 162.23
				Total	**33**	**100.00**	**194.63**	**51.32**	**6 422.63**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	10	100.00	244.23	34.53	2 442.34
				Total	**10**	**100.00**	**244.23**	**34.53**	**2 442.34**
May - Aug 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	17	73.91	143.72	41.35	2 443.30
				Monopril® 20mg	6	26.09	159.19	138.48	955.14
				Total	**23**	**100.00**	**147.76**	**75.17**	**3 398.44**
	Generic	Single agent	**Fosinopril**	Merck-Fosinopril® 10mg	7	70.00	127.14	7.85	889.99
				Merck-Fosinopril® 20mg	3	30.00	177.09	0.00	531.27
				Total	**10**	**100.00**	**142.13**	**24.97**	**1 421.26**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	11	100.00	237.28	40.14	2 610.11
				Total	**11**	**100.00**	**237.28**	**40.14**	**2 610.11**
Sep - Dec 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	6	75.00	149.64	15.09	897.82
				Monopril® 20mg	2	25.00	177.16	0.00	354.32
				Total	**8**	**100.00**	**156.52**	**18.03**	**1 252.14**
	Generic	Single agent	**Fosinopril**	Merck-Fosinopril® 10mg	12	80.00	130.11	0.00	1 561.35
				Merck-Fosinopril® 20mg	3	20.00	177.09	0.00	531.27
				Total	**15**	**100.00**	**139.51**	**19.45**	**2 092.62**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	9	100.00	265.70	13.14	2 391.26
				Total	**9**	**100.00**	**265.70**	**13.14**	**2 391.26**

Table B5 (continued): Cost and prevalence of Fosinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	29	87.88	181.39	26.95	5 260.40
				Monopril® 20mg	4	12.12	290.56	85.75	1 162.23
				Total	**33**	**100.00**	**194.63**	**51.32**	**6 422.63**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	10	100.00	244.23	34.53	2 442.34
				Total	**10**	**100.00**	**244.23**	**34.53**	**2 442.34**
May - Aug 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	17	73.91	143.72	41.35	2 443.30
				Monopril® 20mg	6	26.09	159.19	138.48	955.14
				Total	**23**	**100.00**	**147.76**	**75.17**	**3 398.44**
	Generic	Single agent	**Fosinopril**	Merck-Fosinopril® 10mg	7	70.00	127.14	7.85	889.99
				Merck-Fosinopril® 20mg	3	30.00	177.09	0.00	531.27
				Total	**10**	**100.00**	**142.13**	**24.97**	**1 421.26**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	11	100.00	237.28	40.14	2 610.11
				Total	**11**	**100.00**	**237.28**	**40.14**	**2 610.11**
Sep - Dec 2006	Innovator	Single agent	**Fosinopril**	Monopril® 10mg	6	75.00	149.64	15.09	897.82
				Monopril® 20mg	2	25.00	177.16	0.00	354.32
				Total	**8**	**100.00**	**156.52**	**18.03**	**1 252.14**
	Generic	Single agent	**Fosinopril**	Merck-Fosinopril® 10mg	12	80.00	130.11	0.00	1 561.35
				Merck-Fosinopril® 20mg	3	20.00	177.09	0.00	531.27
				Total	**15**	**100.00**	**139.51**	**19.45**	**2 092.62**
	Innovator	Combination	**Fosinopril/HCTZ**	Monozide® 20/12.5mg	9	100.00	265.70	13.14	2 391.26
				Total	**9**	**100.00**	**265.70**	**13.14**	**2 391.26**

Table B6: Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	2306	40.75	161.52	21.75	372 458.14
				Zestril® 20mg	1697	29.99	275.46	61.74	467 449.07
				Zestril® 5mg	1053	18.61	110.96	22.74	116 839.66
				Prinivil® 20mg	267	4.72	200.96	68.30	53 657.45
				Prinivil® 10mg	224	3.96	109.44	28.22	24 514.44
				Prinivil® 5mg	112	1.98	86.94	28.05	9 737.17
				Total	**5659**	**100.01**	**184.60**	**76.32**	**1 044 655.93**
	Generic	Single agent	**Lisinopril**	Zestomax® 10mg	6588	43.83	112.45	17.73	740 811.72
				Zestomax® 20mg	5797	38.57	181.41	33.27	1 051 656.73
				Zestomax® 5mg	2646	17.60	58.38	41.32	154 480.37
				Total	**15031**	**100.00**	**129.53**	**54.06**	**1 946 948.82**
	Innovator	Combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	9023	62.79	288.08	35.18	2 599 389.49
				Zestoretic® 10/12.5mg	5348	37.21	168.01	20.64	898 491.82
				Total	**14371**	**100.00**	**243.40**	**65.61**	**3 497 881.31**
Year 2004	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	543	24.40	125.54	54.25	68 169.76
				Prinivil® 20mg	504	22.65	91.45	19.38	46 089.99
				Zestril® 20mg	384	17.26	222.49	99.78	58 436.28
				Prinivil® 10mg	347	15.60	59.88	16.00	20 777.69
				Zestril® 5mg	330	14.83	92.51	45.39	30 529.38
				Prinivil® 5mg	117	5.26	44.13	13.73	5 163.69
				Total	**2225**	**100.00**	**114.89**	**76.34**	**229 166.79**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Year 2004	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	5796	39.31	100.45	25.29	582 196.95
				Zetomax® 10mg	5742	38.94	62.83	15.34	360 760.81
				Zetomax® 5mg	2416	16.38	44.14	12.77	106 643.02
				Sinopren® 20mg	318	2.16	60.60	13.92	19 271.27
				Hexal-Lisinopril® 20mg	202	1.37	90.11	24.49	18 201.92
				Sinopren® 10mg	181	1.23	43.82	13.94	7 930.54
				Sinopren® 5mg	71	0.48	37.98	21.23	2 696.73
				Renotens® 5mg	12	0.08	21.84	4.26	262.12
				Zemax® 10mg	8	0.05	48.23	3.24	385.83
				Total	**14746**	**100.00**	**74.50**	**29.72**	**1 098 349.19**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Year 2004	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	5406	64.50	250.53	65.12	1 354 353.45
				Zestoretic® 10/12.5mg	2976	35.50	153.25	30.23	456 070.21
				Total	**8382**	**100.00**	**215.99**	**72.30**	**1 810 423.66**
Year 2005	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	240	32.70	81.68	40.73	19 603.38
				Zestril® 5mg	130	17.71	60.70	40.10	7 891.35
				Zestril® 20mg	110	14.99	136.28	97.99	1 4991.30
				Prinivil® 20mg	108	14.71	70.72	14.11	7 638.23
				Prinivil® 10mg	90	12.26	56.35	20.22	5 071.19
				Prinivil® 5mg	56	7.63	34.21	3.10	1 915.80
				Total	**734**	**100.00**	**77.47**	**55.54**	**57 111.25**
	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	2135	36.43	80.06	23.32	170 933.87
				Zetomax®10mg	1959	33.43	50.55	8.10	99 031.76
				Zetomax® 5mg	683	11.66	35.55	8.47	24 279.24
				Sinopren® 20mg	367	6.26	58.81	8.42	21 583.45
				Hexal-Lisinopril® 20mg	366	6.25	71.14	13.37	26 035.72
				Sinopren®10mg	235	4.01	41.22	5.51	9 685.78
				Sinopren® 5mg	77	1.31	28.82	4.56	2 219.22
				Renotens® 5mg	14	0.24	18.20	0.47	254.86
				Zemax® 5mg	13	0.22	28.73	3.47	373.49
				Zemax® 10mg	9	0.15	50.24	16.63	452.20
				Austell-Lisinopril® 20mg	2	0.03	153.40	0.00	306.80
				Total	**5860**	**99.99**	**60.69**	**23.15**	**355 156.39**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Year 2005	Innovator	Combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	1648	62.21	190.13	68.99	313 327.65
				Zestoretic® 10/12.5mg	1001	37.79	116.05	33.18	116 164.11
				Total	**2649**	**100.00**	**162.13**	**68.32**	**429 491.76**
	Generic	Combination	**Lisinopril/HCTZ**	Listoretic®20/12.5mg	232	46.87	106.00	17.85	24 591.63
				Listoretic® 10/12.5mg	106	21.41	67.55	17.71	7 159.78
				Zetomax Co® 20/12.5mg	90	18.18	114.17	28.59	10 275.59
				Zetomax Co® 10/12.5mg	48	9.70	73.75	16.03	3 540.15
				Hexal-Lisinopril Co® 20/12.5mg	15	3.03	125.01	46.47	1 875.13
				Zetomax Co® 20/25mg	3	0.61	128.86	23.66	386.58
				Hexal-Lisinopril Co® 10/12.5mg	1	0.20	65.26	0.00	65.26
				Total	**495**	**100.00**	**96.76**	**28.52**	**47 894.12**
Year 2006	Innovator	Single agent	**Lisinopril**	Zestril® 5mg	36	32.14	54.54	21.20	1 963.59
				Zestril® 10mg	35	31.25	69.28	6.71	2 424.68
				Zestril® 20mg	25	22.32	121.33	53.43	3 033.13
				Prinivil® 20mg	10	8.93	76.37	1.71	763.71
				Prinivil® 10mg	6	5.36	55.58	0.00	333.48
				Total	**112**	**100.00**	**76.06**	**37.70**	**8 518.59**
	Generic	Single agent	**Lisinopril**	Zetomax® 10mg	352	40.41	61.02	12.42	21 479.21
				Zetomax® 20mg	330	37.89	91.95	24.78	30 343.12
				Zetomax® 5mg	118	13.55	40.66	10.41	4 797.60
				Sinopren® 20mg	39	4.48	64.93	6.88	2 532.23
				Sinopren® 10mg	18	2.07	44.93	14.63	808.80
				Hexal-Lisinopril® 20mg	7	0.80	75.33	6.05	527.32
				Zemax® 20mg	3	0.34	72.24	3.22	216.73
				Austell-Lisinopril® 20mg	2	0.23	153.40	0.00	306.80
				Zemax® 10mg	2	0.23	53.63	7.67	107.26
				Total	**871**	**100.00**	**70.17**	**26.05**	**61 119.07**

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	259	61.96	131.33	44.75	34 014.47
				Zestoretic® 10/12.5mg	159	38.04	75.36	20.78	11 981.53
				Total	**418**	**100.00**	**110.04**	**46.29**	**45 996.00**
	Generic	Combination	**Lisinopril/HCTZ**	Listoretic® 10/12.5mg	378	33.93	66.89	6.17	25 284.22
				Listoretic® 20/12.5mg	356	31.96	109.35	8.87	38 930.14
				Zetomax Co® 20/12.5mg	191	17.15	117.86	13.43	22 510.99
				Zetomax Co® 10/12.5mg	83	7.45	84.88	33.14	7 044.75
				Hexal-Lisinopril Co® 20/12.5mg	70	6.28	132.93	39.82	9 305.10
				Hexal-Lisinopril Co® 10/12.5mg	22	1.97	69.49	4.35	1 528.83
				Zetomax Co® 20/25mg	14	1.26	124.73	0.92	1 746.19
				Total	**1114**	**100.00**	**95.47**	**28.18**	**106 350.22**
Jan - Apr 2004	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	229	27.76	144.06	49.58	32 989.24
				Zestril® 20mg	198	24.00	238.39	87.81	47 201.26
				Zestril® 5mg	140	16.97	103.34	39.69	14 468.17
				Prinivil® 20mg	117	14.18	107.33	18.83	12 557.08
				Prinivil® 10mg	106	12.85	70.14	17.34	7 434.35
				Prinivil® 5mg	35	4.24	54.55	15.74	1 909.37
				Total	**825**	**100.00**	**141.28**	**80.84**	**116 559.47**
	Generic	Single agent	**Lisinopril**	Zetomax® 10mg	1877	42.63	75.18	10.06	141 107.07
				Zetomax® 20mg	1751	39.77	118.90	18.15	208 200.88
				Zetomax® 5mg	737	16.74	55.22	9.26	40 699.02
				Sinopren® 10mg	17	0.39	77.47	0.00	1 316.99
				Sinopren® 20mg	12	0.27	111.61	21.01	1 339.36
				Sinopren® 5mg	6	0.14	82.63	31.72	495.78
				Hexal-Lisinopril® 20mg	3	0.07	117.59	0.00	352.77
				Total	**4403**	**100.01**	**89.37**	**28.66**	**393 511.87**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	1731	63.22	308.28	50.34	533 634.69
				Zestoretic® 10/12.5mg	1007	36.78	179.52	25.51	180 781.41
				Total	**2738**	**100.00**	**260.93**	**75.48**	**714 416.10**
May - Aug 2004	Innovator	Single agent	**Lisinopril**	Prinivil® 20mg	181	25.97	92.00	20.09	16 652.77
				Zestril® 10mg	159	22.81	131.78	54.96	20 952.69
				Zestril® 5mg	111	15.93	96.20	50.41	10 677.78
				Prinivil® 10mg	102	14.63	59.18	14.39	6 036.28
				Zestril® 20mg	102	14.63	230.68	92.78	23 529.40
				Prinivil® 5mg	42	6.03	42.38	11.09	1 779.89
				Total	**697**	**100.00**	**114.25**	**73.97**	**79 628.81**
	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	1927	39.69	104.10	25.59	200 607.65
				Zetomax® 10mg	1831	37.71	64.57	14.70	118 232.32
				Zetomax® 5mg	782	16.11	46.30	11.12	36 209.08
				Hexal-Lisinopril® 20mg	198	4.08	89.82	24.44	17 783.76
				Sinopren® 20mg	63	1.30	65.38	17.49	4 118.80
				Sinopren® 10mg	41	0.84	45.68	15.49	1 873.07
				Sinopren® 5mg	11	0.23	49.48	27.30	544.32
				Renotens® 5mg	2	0.04	21.72	0.00	43.44
				Total	**4855**	**100.00**	**78.15**	**30.22**	**379 412.44**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	1704	64.59	249.15	55.37	424 553.85
				Zestoretic® 10/12.5mg	934	35.41	149.79	21.49	139 903.87
				Total	**2638**	**100.00**	**213.97**	**66.35**	**564 457.72**

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Innovator	Single agent	**Lisinopril**	Prinivil® 20mg	206	29.30	81.94	11.48	16 880.14
				Zestril® 10mg	155	22.05	91.79	43.89	14 227.83
				Prinivil® 10mg	139	19.77	52.57	11.25	7 307.06
				Zestril® 20mg	84	11.95	175.07	119.17	14 705.62
				Zestril® 5mg	79	11.24	68.14	38.33	5 383.43
				Prinivil® 5mg	40	5.69	36.86	7.78	1 474.43
				Total	**703**	**100.00**	**84.90**	**60.51**	**59 978.51**
	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	2118	38.59	81.86	15.59	173 388.42
				Zetomax® 10mg	2034	37.06	49.86	8.07	101 421.42
				Zetomax® 5mg	897	16.34	33.15	5.92	29 734.92
				Sinopren® 20mg	243	4.43	56.84	2.51	13 813.11
				Sinopren ®10mg	123	2.24	38.54	4.57	4 740.48
				Sinopren® 5mg	54	0.98	30.68	7.23	1 656.63
				Renotens® 5mg	10	0.18	21.87	4.71	218.68
				Zemax® 10mg	8	0.15	48.23	3.24	385.83
				Hexal-Lisinopri ®20mg	1	0.02	65.39	0.00	65.39
				Total	**5488**	**99.99**	**59.30**	**22.07**	**325 424.88**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	1971	65.57	201.00	37.06	396 164.91
				Zestoretic® 10/12.5mg	1035	34.43	130.81	19.81	135 384.93
				Total	**3006**	**100.00**	**176.83**	**46.35**	**531 549.84**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	92	32.97	88.99	45.80	8 187.13
				Zestril® 5mg	47	16.85	68.37	44.69	3 213.51
				Prinivil® 20mg	43	15.41	74.75	11.77	3 212.93
				Zestril® 20mg	43	15.41	124.13	74.81	5 337.66
				Prinivil® 10mg	32	11.47	54.41	17.25	1 741.13
				Prinivil® 5mg	22	7.89	32.61	2.68	717.51
				Total	**279**	**100.00**	**80.13**	**50.07**	**22 409.87**
	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	724	40.33	80.06	20.34	57 962.85
				Zetomax® 10mg	618	34.43	50.03	7.41	30 916.38
				Zetomax® 5mg	223	12.42	34.91	9.21	7 784.44
				Sinopren® 20mg	120	6.69	57.71	2.36	6 924.79
				Sinopren® 10mg	65	3.62	39.32	3.84	2 555.78
				Sinopren® 5mg	37	2.06	29.35	1.71	1 085.79
				Renotens® 5mg	5	0.28	18.43	0.19	92.16
				Zemax® 10mg	3	0.17	61.97	27.91	185.92
				Total	**1795**	**100.00**	**59.56**	**22.65**	**107 508.11**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	620	63.33	213.35	53.54	132 277.13
				Zestoretic® 10/12.5mg	359	36.67	133.16	23.14	47 806.10
				Total	**979**	**100.00**	**183.95**	**59.20**	**180 083.23**
May - Aug 2005	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	88	33.98	87.42	43.70	7 693.13
				Zestril® 5mg	48	18.53	65.98	44.80	3 167.05
				Zestril® 20mg	37	14.29	156.45	128.74	5 788.49
				Prinivil® 20mg	34	13.13	68.26	14.31	2 320.73
				Prinivil® 10mg	29	11.2	55.68	19.24	1 614.84
				Prinivil® 5mg	23	8.88	35.12	3.25	807.80
				Total	**259**	**100.01**	**82.32**	**67.19**	**21 392.04**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2005	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	769	36.32	81.60	22.18	62 753.32
				Zetomax® 10mg	714	33.73	50.53	7.48	36 080.68
				Zetomax® 5mg	242	11.43	34.96	6.84	8 461.16
				Sinopren® 20mg	143	6.75	58.92	9.88	8 424.89
				Hexal-Lisinopril® 20mg	112	5.29	72.07	11.15	8 071.56
				Sinopren® 10mg	91	4.30	41.55	6.31	3 781.42
				Sinopren® 5mg	27	1.28	28.56	6.35	771.19
				Renotens® 5mg	9	0.43	18.08	0.53	162.70
				Zemax® 5mg	7	0.33	28.02	3.69	196.13
				Zema®x 10mg	2	0.09	47.09	0.00	94.18
				Austell-Lisinopril® 20mg	1	0.05	153.40	0.00	153.40
				Total	**2117**	**100.00**	**61.03**	**23.18**	**128 950.63**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	624	63.80	214.75	59.33	134 002.04
				Zestoretic® 10/12.5mg	354	36.20	130.60	23.51	46 233.82
				Total	**978**	**100.00**	**184.29**	**63.88**	**180 235.86**
	Generic	combination	**Lisinopril/HCTZ**	Listoretic® 20/12.5mg	52	52.53	125.49	14.42	6 525.59
				Zetomax Co® 20/12.5mg	20	20.20	133.65	10.88	2 672.91
				Listoretic® 10/12.5mg	13	13.13	86.90	27.28	1 129.75
				Zetomax Co® 10/12.5mg	13	13.13	85.25	6.29	1 108.26
				Zetomax Co® 20/25mg	1	1.01	137.64	0.00	137.64
				Total	**99**	**100.00**	**116.91**	**24.09**	**11 574.15**
Sep - Dec 2005	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	60	30.61	62.05	12.09	3 723.12
				Zestril® 5mg	35	17.86	43.17	13.67	1 510.79
				Prinivil® 20mg	31	15.82	67.89	15.89	2 104.57
				Zestril® 20mg	30	15.31	128.84	81.36	3 865.15
				Prinivil® 10mg	29	14.80	59.15	24.24	1 715.22
				Prinivi®l 5mg	11	5.61	35.50	2.23	390.49
				Total	**196**	**100.01**	**67.41**	**44.12**	**13 309.34**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	642	32.96	78.22	27.34	50 217.70
				Zetomax® 10mg	627	32.19	51.09	9.32	32 034.70
				Hexal-Lisinopril® 20mg	254	13.04	70.73	14.24	17 964.16
				Zetomax® 5mg	218	11.19	36.85	9.16	8 033.64
				Sinopren® 20mg	104	5.34	59.94	10.39	6 233.77
				Sinopren® 10mg	79	4.06	42.39	5.35	3 348.58
				Sinopren® 5mg	13	0.67	27.86	5.78	362.24
				Zemax® 5mg	6	0.31	29.56	3.30	177.36
				Zemax® 10mg	4	0.21	43.03	2.10	172.10
				Austell-Lisinopri®l 20mg	1	0.05	153.40	0.00	153.40
				Total	**1948**	**100.02**	**60.93**	**23.53**	**118 697.65**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	404	58.38	116.46	49.00	47 048.48
				Zestoretic® 10/12.5mg	288	41.62	76.82	17.80	22 124.19
				Total	**692**	**100.00**	**99.96**	**43.75**	**69 172.67**
	Generic	combination	**Lisinopril/HCTZ**	Listoretic® 20/12.5mg	180	45.45	100.37	14.47	18 066.04
				Listoretic® 10/12.5mg	93	23.48	64.84	14.16	6 030.03
				Zetomax Co® 20/12.5mg	70	17.68	108.61	29.67	7 602.68
				Zetomax Co® 10/12.5mg	35	8.84	69.48	16.49	2 431.89
				Hexal-Lisinopril Co® 20/12.5mg	15	3.79	125.01	46.47	1 875.13
				Zetomax Co® 20/25mg	2	0.51	124.47	31.69	248.94
				Hexal-Lisinopril Co® 10/12.5mg	1	0.25	65.26	0.00	65.26
				Total	**396**	**100.00**	**91.72**	**27.31**	**36 319.97**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2006	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	12	28.57	70.58	6.81	846.97
				Zestril® 20mg	12	28.57	114.28	58.55	1 371.38
				Zestril® 5mg	11	26.19	54.70	22.94	601.71
				Prinivil® 10mg	4	9.52	55.58	0.00	222.32
				Prinivil® 20mg	3	7.14	75.83	0.00	227.49
				Total	**42**	**99.99**	**77.85**	**40.71**	**10 096.53**
	Generic	Single agent	**Lisinopril**	Zetomax® 20mg	114	40.14	91.33	25.60	10 411.11
				Zetomax® 10mg	111	39.08	61.81	13.28	6 860.87
				Zetomax® 5mg	39	13.73	38.41	4.84	1 497.82
				Sinopren® 20mg	12	4.23	67.44	5.56	809.32
				Sinopren® 10mg	6	2.11	40.29	1.75	241.74
				Austell-Lisinopril® 20mg	2	0.70	153.40	0.00	306.80
				Total	**284**	**99.99**	**70.87**	**27.37**	**20 127.66**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	91	61.90	128.06	32.81	11 653.52
				Zestoretic® 10/12.5mg	56	38.10	74.37	21.48	4 164.76
				Total	**147**	**100.00**	**107.61**	**39.01**	**15 818.28**
	Generic	combination	**Lisinopril/HCTZ**	Listoretic® 10/12.5mg	96	32.99	66.66	0.68	6 399.69
				Listoretic® 20/12.5mg	89	30.58	109.35	5.26	9 732.34
				Zetomax Co® 20/12.5mg	41	14.09	115.16	7.30	4 721.75
				Hexal-Lisinopril Co® 20/12.5mg	30	10.31	134.21	40.39	4 026.22
				Zetomax Co® 10/12.5mg	19	6.53	66.65	7.06	1 266.31
				Hexal-Lisinopril Co® 10/12.5mg	8	2.75	70.91	3.38	567.27
				Zetomax Co® 20/25mg	8	2.75	125.06	0.00	1 000.46
				Total	**291**	**100.00**	**95.24**	**28.66**	**27 714.04**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/item (R)	Standard deviation(±)	Total cost (R)
May-Aug 2006	Innovator	Single agent	**Lisinopril**	Zestril® 5mg	15	39.47	58.25	26.22	873.80
				Zestril® 10mg	10	26.32	67.39	6.99	673.89
				Zestril ®20mg	7	18.42	131.24	48.23	918.71
				Prinivil® 20mg	4	10.53	77.18	2.71	308.73
				Prinivil® 10mg	2	5.26	55.58	0.00	111.16
				Total	**38**	**100.00**	**75.96**	**37.39**	**2 886.29**
	Generic	Single agent	**Lisinopril**	Zetomax® 10mg	118	40.00	61.03	11.19	7 201.34
				Zetomax® 20mg	103	34.92	94.09	27.92	9 690.88
				Zetomax® 5mg	45	15.25	41.58	11.53	1 871.01
				Sinopren® 20mg	17	5.76	60.79	6.74	1 033.45
				Hexal-Lisinopril® 20mg	7	2.37	95.29	35.61	667.05
				Sinopren® 10mg	4	1.36	39.39	0.00	157.56
				Zemax® 20mg	1	0.34	70.38	0.00	70.38
				Total	**295**	**100.00**	**69.67**	**26.85**	**20 551.94**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	86	62.77	129.60	41.47	11 145.88
				Zestoretic® 10/12.5mg	51	37.23	71.78	15.07	3 660.63
				Total	**137**	**100.00**	**108.08**	**44.11**	**14 806.51**
	Generic	combination	**Lisinopril/HCTZ**	Listoretic® 10/12.5mg	137	35.49	67.27	7.95	9 216.03
				Listoretic® 20/12.5mg	121	31.35	109.24	8.35	13 218.52
				Zetomax Co® 20/12.5mg	64	16.58	117.73	3.48	7 534.91
				Zetomax Co® 10/12.5mg	29	7.51	77.42	26.90	1 871.01
				Hexal-Lisinopril Co® 20/12.5mg	23	5.96	133.87	40.23	3 078.98
				Hexal-Lisinopril Co® 10/12.5mg	7	1.81	68.00	5.10	476.01
				Zetomax Co® 20/25mg	5	1.30	124.13	1.44	620.67
				Total	**386**	**100.00**	**94.28**	**27.43**	**36 390.26**

Table B6 (continued): Cost and prevalence of Lisinopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Innovator	Single agent	**Lisinopril**	Zestril® 10mg	13	40.63	69.52	6.60	903.82
				Zestril® 5mg	10	31.25	48.81	5.78	488.08
				Zestril® 20mg	6	18.75	123.84	55.69	743.04
				Prinivil® 20mg	3	9.38	75.83	0.00	227.49
				Total	**32**	**100.01**	**73.83**	**34.94**	**2 362.43**
	Generic	Single agent	**Lisinopril**	Zetomax® 10mg	123	42.12	60.30	12.81	7 417.00
				Zetomax® 20mg	113	38.7	90.63	20.66	10 241.13
				Zetomax® 5mg	34	11.64	42.02	13.08	1 428.77
				Sinopren® 20mg	10	3.42	68.95	4.76	689.46
				Sinopren® 10mg	8	2.74	51.19	20.91	409.50
				Zemax® 10mg	2	0.68	53.63	7.67	107.26
				Zemax ®20mg	2	0.68	73.18	3.95	146.35
				Total	**292**	**99.98**	**70.00**	**23.92**	**20 439.47**
	Innovator	combination	**Lisinopril/HCTZ**	Zestoretic® 20/12.5mg	82	61.19	136.77	57.73	11 215.07
				Zestoretic® 10/12.5mg	52	38.81	79.93	24.15	4 156.14
				Total	**134**	**100.00**	**114.71**	**55.01**	**15 371.21**
	Generic	combination	**Lisinopril/HCTZ**	Listoretic® 20/12.5mg	146	33.41	109.48	10.87	15 979.28
				Listoretic® 10/12.5mg	145	33.18	66.68	6.28	9 668.50
				Zetomax Co® 20/12.5mg	86	19.68	119.24	19.07	10 254.33
				Zetomax Co® 10/12.5mg	35	8.01	100.95	39.08	3 533.30
				Hexal-Lisinopril Co® 20/12.5mg	17	3.89	129.41	40.48	2 199.90
				Hexal-Lisinopril Co® 10/12.5mg	7	1.60	69.36	4.66	485.55
				Zetomax Co® 20/25mg	1	0.23	125.06	0.00	125.06
				Total	**437**	**100.00**	**96.67**	**28.53**	**42 245.92**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B7: Cost and prevalence of Moexipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	9	100.00	124.97	0.93	1 124.73
				Total	**9**	**100.00**	**124.97**	**0.93**	**1 124.73**
Year 2004	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	536	67.76	121.00	14.62	64 854.86
				Perdix® 15mg	255	32.24	200.50	17.36	51 128.39
				Total	**791**	**100.00**	**146.63**	**40.30**	**115 983.25**
Year 2005	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	508	58.12	116.64	18.42	59 252.80
				Perdix® 15mg	366	41.88	199.37	30.30	72 970.20
				Total	**874**	**100.00**	**151.28**	**47.42**	**132 223.00**
Year 2006	Innovator	Single agent	**Moexipril**	Perdix® 15mg	361	51.50	199.39	29.22	71 979.46
				Perdix® 7.5mg	340	48.50	114.03	8.51	38 770.12
				Total	**701**	**100.00**	**157.99**	**47.92**	**110 749.58**
Jan - Apr 2004	Innovator	Single agent	**Moexipril**	Perdix ®7.5mg	88	84.62	125.45	1.22	11 039.26
				Perdix® 15mg	16	15.38	208.16	1.01	3 330.49
				Total	**104**	**100.00**	**138.17**	**30.01**	**14 369.75**

Table B7 (continued): Cost and prevalence of Moexipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2004	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	228	66.67	125.78	9.58	28 678.75
				Perdix® 15mg	114	33.33	206.38	10.44	23 527.52
				Total	**342**	**100.00**	**152.65**	**39.31**	**52 206.27**
Sep - Dec 2004	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	220	63.77	114.26	18.69	25 136.85
				Perdix® 15mg	125	36.23	194.16	20.93	24 270.38
				Total	**345**	**100.00**	**143.21**	**43.12**	**49 407.23**
Jan - Apr 2005	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	179	62.37	119.95	25.87	21 470.49
				Perdix® 15mg	108	37.63	201.58	35.45	21 770.76
				Total	**287**	**100.00**	**150.67**	**49.56**	**43 241.25**
May - Aug 2005	Innovator	Single agent	**Moexipril**	Perdix ®7.5mg	181	56.21	114.63	11.81	20 747.79
				Perdix® 15mg	141	43.79	200.08	33.84	28 210.63
				Total	**322**	**100.00**	**152.04**	**48.79**	**48 958.42**
Sep - Dec 2005	Innovator	Single agent	**Moexipril**	Perdix ®7.5mg	148	55.85	115.10	12.96	17 034.52
				Perdix® 15mg	117	44.15	196.49	18.28	22 988.81
				Total	**265**	**100.00**	**151.03**	**43.36**	**40 023.33**
Jan - Apr 2006	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	128	50.20	114.37	9.92	14 639.88
				Perdix® 15mg	127	49.80	200.77	32.28	25 497.54
				Total	**255**	**100.00**	**157.40**	**49.39**	**40 137.42**
May - Aug 2006	Innovator	Single agent	**Moexipril**	Perdix® 7.5mg	124	51.24	114.19	9.84	14 159.35
				Perdix® 15mg	118	48.76	199.72	26.31	23 566.85
				Total	**242**	**100.00**	**155.89**	**47.12**	**37 726.20**
Sep - Dec 2006	Innovator	Single agent	**Moexipril**	Perdix® 15mg	116	56.86	197.54	28.66	22 915.07
				Perdix® 7.5mg	88	43.14	113.31	1.08	99 70.89
				Total	**204**	**100.00**	**161.21**	**47.06**	**328 85.96**

Table B8: Cost and prevalence of Perindopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Perindopril**	Coversyl®	30031	100.00	217.39	52.89	6 528 300.76
				Total	**30031**	**100.00**	**217.39**	**52.89**	**6 528 300.76**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	12378	100.00	241.99	35.21	2 995 329.77
				Total	**12378**	**100.00**	**241.99**	**35.21**	**2 995 329.77**
Year 2004	Innovator	Single agent	**Perindopril**	Coversyl®	12793	100.00	167.92	68.38	2 148 208.06
				Total	**12793**	**100.00**	**167.92**	**68.38**	**2 148 208.06**
	Generic	Single agent	**Perindopril**	Prexum®	20959	100.00	137.20	35.76	2 875 557.50
				Total	**20959**	**100.00**	**137.20**	**35.76**	**2 875 557.50**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	25926	94.84	210.89	36.24	5 467 572.61
				Preterax®	1411	5.16	197.98	31.06	279 352.79
				Total	**27337**	**100.00**	**210.23**	**36.11**	**5 746 925.40**
Year 2005	Innovator	Single agent	**Perindopril**	Coversyl®	5778	100.00	140.24	41.95	810 301.65
				Total	**5778**	**100.00**	**140.24**	**41.95**	**810 301.65**
	Generic	Single agent	**Perindopril**	Prexum®	20577	100.00	144.02	37.74	2 963 546.15
				Total	**20577**	**100.00**	**144.02**	**37.74**	**2 963 546.15**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	21724	91.14	211.17	39.18	4 587 526.46
				Preterax®	2111	8.86	201.90	30.98	426 210.80
				Total	**23835**	**100.00**	**210.35**	**38.62**	**5 013 737.26**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax®	21	100.00	225.29	10.17	4 731.05
				Total	**21**	**100.00**	**225.29**	**10.17**	**4 731.05**

Table B8 (continued): Cost and prevalence of Perindopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Single agent	**Perindopril**	Coversyl® 4mg	3014	92.94	150.92	37.94	454 859.78
				Coversyl® 10mg	229	7.06	281.65	94.30	64 497.73
				Total	**3243**	**100.00**	**160.15**	**55.54**	**519 357.51**
	Generic	Single agent	**Perindopril**	Prexum®	14327	100.00	155.75	36.82	2 231 373.27
				Total	**14327**	**100.00**	**155.75**	**36.82**	**2 231 373.27**
	Innovator	Combination	**Indapamide/ Perindopril**	Prexum Plus®	9186	45.59	183.10	33.37	1 681 971.99
				Coversyl Plus®	9161	45.46	219.06	39.76	2 006 796.07
				Preterax®	1804	8.95	214.44	22.41	386 846.58
				Total	**20151**	**100.00**	**202.25**	**39.75**	**4 075 614.64**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax®	106	100.00	216.79	20.65	22 979.56
				Total	**106**	**100.00**	**216.79**	**20.65**	**22 979.56**
Jan - Apr 2004	Innovator	Single agent	**Perindopril**	Coversyl®	3832	100.00	182.19	66.60	698 167.31
				Total	**3832**	**100.00**	**182.19**	**66.60**	**698 167.31**
	Generic	Single agent	**Perindopril**	Prexum®	3618	100.00	152.43	39.52	551 480.92
				Total	**3618**	**100.00**	**152.43**	**39.52**	**551 480.92**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	6133	97.26	230.18	32.80	1 411 674.50
				Preterax ®	173	2.74	211.12	32.73	36 524.36
				Total	**6306**	**100.00**	**229.65**	**32.95**	**1 448 198.86**
May - Aug 2004	Innovator	Single agent	**Perindopril**	Coversyl®	5049	100.00	187.62	68.12	947 309.90
				Total	**5049**	**100.00**	**187.62**	**68.12**	**947 309.90**
	Generic	Single agent	**Perindopril**	Prexum®	6528	100.00	137.50	36.33	897 603.98
				Total	**6528**	**100.00**	**137.50**	**36.33**	**897 603.98**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	8838	94.58	217.90	33.90	1 925 802.02
				Preterax®	506	5.42	205.66	29.31	104 065.05
				Total	**9344**	**100.00**	**217.24**	**33.78**	**2 029 867.07**

Table B8 (continued): Cost and prevalence of Perindopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Innovator	Single agent	**Perindopril**	Coversyl®	3912	100.00	128.51	52.00	502 730.85
				Total	**3912**	**100.00**	**128.51**	**52.00**	**502 730.85**
	Generic	Single agent	**Perindopril**	Prexum®	10813	100.00	131.92	32.47	1 426 472.60
				Total	**10813**	**100.00**	**131.92**	**32.47**	**1 426 472.60**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	10955	93.74	194.44	32.57	2 130 096.09
				Preterax®	732	6.26	189.57	29.37	138 763.38
				Total	**11687**	**100.00**	**194.14**	**32.40**	**2 268 859.47**
Jan - Apr 2005	Innovator	Single agent	**Perindopril**	Coversyl®	1956	100.00	137.33	40.91	268 616.43
				Total	**1956**	**100.00**	**137.33**	**40.91**	**268 616.43**
	Generic	Single agent	**Perindopril**	Prexum®	5934	100.00	141.89	37.60	841 986.98
				Total	**5934**	**100.00**	**141.89**	**37.60**	**841 986.98**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	6512	91.95	207.70	34.58	1 352 540.31
				Preterax®	570	8.05	201.20	26.56	114 681.68
				Total	**7082**	**100.00**	**207.18**	**34.05**	**1 467 221.99**
May - Aug 2005	Innovator	Single agent	**Perindopril**	Coversyl®	2026	100.00	139.87	44.56	283 382.45
				Total	**2026**	**100.00**	**139.87**	**44.56**	**283 382.45**
	Generic	Single agent	**Perindopril**	Prexum®	7342	100.00	143.98	40.67	1 057 110.49
				Total	**7432**	**100.00**	**143.98**	**40.67**	**1 057 110.49**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	7705	91.33	210.94	41.03	1 625 329.22
				Preterax®	731	8.67	200.88	31.32	146 843.65
				Total	**8436**	**100.00**	**210.07**	**40.38**	**1 772 172.87**

Table B8 (continued): Cost and prevalence of Perindopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Single agent	**Perindopril**	Coversyl®	1796	100.00	143.82	39.73	258 302.77
				Total	**1796**	**100.00**	**143.82**	**39.73**	**258 302.77**
	Generic	Single agent	**Perindopril**	Prexum®	7301	100.00	145.79	34.57	1 064 448.68
				Total	**7301**	**100.00**	**145.79**	**34.57**	**1 064 448.68**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	7507	90.26	214.42	40.70	1 609 656.93
				Preterax®	810	9.74	203.32	33.43	164 685.47
				Total	**8317**	**100.00**	**213.34**	**40.19**	**1 774 342.40**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax®	21	100.00	225.29	10.17	4 731.05
				Total	**21**	**100.00**	**225.29**	**10.17**	**4 731.05**
Jan-Apr 2006	Innovator	Single agent	**Perindopril**	Coversyl®	1048	100.00	149.11	35.32	156 263.94
				Total	**1048**	**100.00**	**149.11**	**35.32**	**156 263.94**
	Generic	Single agent	**Perindopril**	Prexum®	4701	100.00	156.41	42.88	735 282.17
				Total	**4701**	**100.00**	**156.41**	**42.88**	**735 282.17**
	Innovator	Combination	**Indapamide/ Perindopril**	Coversyl Plus®	4256	72.63	223.72	37.32	952 169.30
				Prexum Plus®	1016	17.34	182.97	44.77	185 897.85
				Preterax®	558	10.03	214.94	21.94	126 382.23
				Total	**5860**	**100.00**	**215.78**	**40.49**	**1 264 449.38**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax®	45	100.00	224.37	15.01	10 096.53
				Total	**45**	**100.00**	**224.37**	**15.01**	**10 096.53**

Table B8 (continued): Cost and prevalence of Perindopril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May-Aug 2006	Innovator	Single agent	**Perindopril**	Coversyl® 4mg	1045	97.85	150.14	37.93	156 894.09
				Coversyl® 10mg	23	2.15	272.05	18.64	6 257.14
				Total	**1068**	**100.00**	**152.76**	**41.57**	**163 151.23**
	Generic	Single agent	**Perindopril**	Prexum®	4870	100.00	155.38	35.01	756 719.35
				Total	**4870**	**100.00**	**155.38**	**1071.29**	**756 719.35**
	Innovator	Combination	**Indapamide/ Perindopril**	Prexum Plus®	3530	51.65	182.80	35.75	645 277.44
				Coversyl Plus®	2695	39.44	213.20	39.20	574 562.18
				Preterax®	609	8.91	214.41	25.93	130 573.47
				Total	**6834**	**100.00**	**197.60**	**39.50**	**1 350 413.09**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax®	29	100.00	209.02	23.51	6 061.63
				Total	**29**	**100.00**	**209.02**	**23.51**	**6 061.63**
Sep - Dec 2006	Innovator	Single agent	**Perindopril**	Coversyl® 4mg	921	81.72	153.86	40.61	141 701.75
				Coversyl ®10mg	206	18.28	282.72	99.20	58 240.59
				Total	**1127**	**100.00**	**177.41**	**74.98**	**199 942.34**
	Generic	Single agent	**Perindopril**	Prexum®	4756	100.00	155.46	31.82	739 371.75
				Total	**4756**	**100.00**	**155.46**	**31.82**	**739 371.75**
	Innovator	Combination	**Indapamide/ Perindopril**	Prexum Plus®	4640	62.22	183.36	28.19	850 796.70
				Coversyl Plus®	2210	29.64	217.22	43.69	480 064.59
				Preterax®	607	8.14	213.99	18.80	129 890.88
				Total	**7457**	**100.00**	**195.89**	**36.71**	**1 460 752.17**
	Generic	Combination	**Indapamide/ Perindopril**	Bipreterax ®	32	100.00	213.17	21.72	6 821.40
				Total	**32**	**100.00**	**213.17**	**21.72**	**6 821.40**

Table B9: Cost and prevalence of Quinapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	Quinapril	Accupril® 10mg	4375	48.86	163.16	32.75	713 836.37
				Accupril® 20mg	2905	32.44	245.55	42.80	713 318.01
				Accupril® 5mg	1316	14.70	116.04	30.85	152 712.97
				Accupril® 40mg	358	4.00	233.03	57.40	834 24.53
				Total	**8954**	**100.00**	**185.76**	**60.02**	**1 663 291.88**
	Innovator	Combination	Quinapril/HCTZ	Accuretic® 20/12.5mg	8865	55.97	241.12	37.63	2 137 571.22
				Accuretic® 10/12.5mg	6974	44.03	158.48	25.96	1 105 207.15
				Total	**15839**	**100.00**	**204.73**	**52.66**	**3 242 778.37**
Year 2004	Innovator	Single agent	Quinapril	Accupril® 10mg	2422	43.8	154.47	41.24	374 127.89
				Accupril® 20mg	1923	34.77	233.59	62.44	449 195.90
				Accupri®l 5mg	649	11.74	111.96	43.29	72 662.17
				Accupril® 40mg	536	9.69	215.35	55.35	115 429.90
				Total	**5530**	**100.00**	**182.90**	**67.50**	**1 011 415.86**
	Innovator	Combination	Quinapril/HCTZ	Accuretic® 20/12.5mg	6679	59.91	234.96	52.03	1 569 267.30
				Accuretic® 10/12.5mg	4470	40.09	160.78	34.65	718 683.64
				Total	**11149**	**100.00**	**205.22**	**58.52**	**2 287 950.94**
Year 2005	Innovator	Single agent	Quinapril	Accupril® 10mg	800	41.39	145.54	52.55	116 430.48
				Accupri®l 20mg	793	41.02	236.75	100.68	187 739.48
				Accupril® 40mg	171	8.85	183.77	39.56	31 424.46
				Accupril® 5mg	169	8.74	88.60	46.93	14 972.84
				Total	**1933**	**100.00**	**181.36**	**90.39**	**350 567.26**
	Innovator	Combination	Quinapril/HCTZ	Accuretic® 20/12.5mg	3187	63.15	215.17	34.95	685 751.49
				Accuretic® 10/12.5mg	1860	36.85	143.78	25.87	267 434.04
				Total	**5047**	**100.00**	**188.86**	**46.95**	**953 185.53**

Table B9 (continued): Cost and prevalence of Quinapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Single agent	**Quinapril**	Accupril® 20mg	143	43.60	248.36	125.07	35 514.86
				Accupril®10mg	136	41.46	127.42	86.51	17 328.66
				Accupri®l 5mg	35	10.67	37.81	59.00	1 323.43
				Accupril® 40mg	14	4.27	214.88	36.47	3 008.37
				Total	**328**	**100.00**	**174.32**	**125.20**	**57 175.32**
	Generic	Single agent	**Quinapril**	Quinaspen® 20mg	48	70.59	146.20	42.63	7 017.64
				Quinaspen® 10mg	20	29.41	84.79	6.82	1 695.84
				Total	**68**	**100.00**	**128.14**	**45.63**	**8 713.48**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	777	56.1	224.80	52.87	174 670.58
				Accuretic® 10/12.5mg	608	43.9	149.26	39.36	90 747.67
				Total	**1385**	**100.00**	**191.64**	**60.44**	**265 418.25**
	Generic	Combination	**Quinapril/HCTZ**	Adco-Quinaretic® 20/12.5mg	241	63.42	131.65	8.51	31 727.80
				Adco-Quinaretic® 10/12.5mg	139	36.58	86.14	6.08	11 973.00
				Total	**380**	**100.00**	**115.00**	**23.26**	**43 700.80**
Jan - Apr 2004	Innovator	Single agent	**Quinapril**	Accupril® 10mg	803	45.21	183.04	33.91	146 984.85
				Accupril® 20mg	598	33.67	278.59	52.70	166 597.81
				Accupril® 5mg	232	13.06	138.00	29.80	32 017.05
				Accupril® 40mg	143	8.05	260.96	62.60	37 316.60
				Total	**1776**	**99.99**	**215.61**	**68.20**	**382 916.31**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	1857	56.62	281.32	46.01	522 405.91
				Accuretic® 10/12.5mg	1423	43.38	187.87	31.00	267 332.49
				Total	**3280**	**100.00**	**240.77**	**61.32**	**789 738.40**
May - Aug 2004	Innovator	Single agent	**Quinapril**	Accupril® 10mg	781	44.71	151.17	37.21	118 066.00
				Accupril® 20mg	609	34.86	231.68	48.02	141 092.47
				Accupril® 5mg	210	12.02	103.40	49.99	217 13.25
				Accupril® 40mg	147	8.41	213.83	47.36	31 433.12
				Total	**1747**	**100.00**	**178.77**	**63.34**	**312 304.84**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	2091	59.39	238.91	47.39	499 559.18
				Accuretic® 10/12.5mg	1430	40.61	158.99	27.71	227 351.63
				Total	**3521**	**100.00**	**206.45**	**56.45**	**726 910.81**

Table B9 (continued): Cost and prevalence of Quinapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Innovator	Single agent	**Quinapril**	Accupril® 10mg	838	41.75	130.16	33.79	109 077.04
				Accupril® 20mg	716	35.68	197.63	56.66	141 505.62
				Accupril® 40mg	246	12.26	189.76	34.78	46 680.18
				Accupril® 5mg	207	10.31	91.46	33.19	18 931.87
				Total	**2007**	**100.00**	**157.55**	**57.85**	**316 194.71**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	2731	62.81	200.40	28.18	547 302.21
				Accuretic® 10/12.5mg	1617	37.19	138.53	25.53	223 999.52
				Total	**4348**	**100.00**	**177.39**	**40.44**	**771 301.73**
Jan - Apr 2005	Innovator	Single agent	**Quinapril**	Accupril® 10mg	292	43.71	146.88	55.07	42 888.61
				Accupril® 20mg	264	39.52	227.20	105.40	59 980.98
				Accupril® 5mg	58	8.68	96.07	55.59	5 571.77
				Accupril® 40mg	54	8.08	182.29	42.95	9 843.56
				Total	**668**	**99.99**	**177.07**	**89.89**	**118 284.92**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	1053	62.53	210.21	37.24	221 352.95
				Accuretic® 10/12.5mg	631	37.47	140.86	25.37	88 880.31
				Total	**1684**	**100.00**	**184.22**	**47.28**	**310 233.26**
May - Aug 2005	Innovator	Single agent	**Quinapril**	Accupril® 10mg	286	41.39	147.31	58.92	42 129.68
				Accupril® 20mg	285	41.24	244.27	102.69	69 616.26
				Accupril® 40mg	66	9.55	187.74	35.67	12 390.81
				Accupril® 5mg	54	7.81	85.36	41.92	4 609.64
				Total	**691**	**99.99**	**186.32**	**94.04**	**128 746.39**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	1135	62.60	217.34	37.61	246 684.45
				Accuretic® 10/12.5mg	678	37.40	142.66	21.69	96 722.00
				Total	**1813**	**100.00**	**189.41**	**48.66**	**343 406.45**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals

Table B9 (continued): Cost and prevalence of Quinapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2005	Innovator	Single agent	**Quinapril**	Accupril® 20mg	244	42.51	238.29	92.31	58 142.24
				Accupril® 10mg	222	38.68	141.50	38.64	31 412.19
				Accupril® 5mg	57	9.93	84.06	41.35	4 791.43
				Accupril® 40mg	51	8.89	180.20	40.91	9 190.09
				Total	**574**	**100.01**	**180.38**	**86.25**	**103 535.95**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	999	64.45	217.93	28.14	217 714.09
				Accuretic® 10/12.5mg	551	35.55	148.51	30.20	81 831.73
				Total	**1550**	**100.00**	**193.23**	**44.03**	**299 545.82**
Jan - Apr 2006	Innovator	Single agent	**Quinapril**	Accupril® 20mg	71	53.38	318.55	131.08	22 617.14
				Accupril® 10mg	47	35.34	159.94	103.73	7 516.96
				Accupril® 5mg	12	9.02	69.22	70.97	830.68
				Accupril® 40mg	3	2.26	257.99	12.40	773.98
				Total	**133**	**100.00**	**238.64**	**146.77**	**31 738.76**
	Generic	Single agent	**Quinapril**	Quinaspen® 10mg	3	50.00	81.66	11.71	244.98
				Quinaspen® 20mg	3	50.00	126.74	8.32	380.22
				Total	**6**	**100.00**	**104.20**	**26.31**	**625.20**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	368	61.23	253.68	30.27	93 354.59
				Accuretic® 10/12.5mg	233	38.77	157.67	33.28	36 738.13
				Total	**601**	**100.00**	**216.46**	**56.40**	**130 092.72**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals

Table B9 (continued): Cost and prevalence of Quinapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2006	Innovator	Single agent	**Quinapril**	Accupril® 10mg	52	50.00	120.75	88.42	6 279.03
				Accupril® 20mg	39	37.50	175.89	53.28	6 859.76
				Accupril ®5mg	7	6.73	1.16	0.00	8.12
				Accupril® 40mg	6	5.77	217.10	37.77	1 302.61
				Total	**104**	**100.00**	**138.94**	**85.54**	**14 449.52**
	Generic	Single agent	**Quinapril**	Quinaspen® 20mg	21	72.41	152.29	51.30	3 198.07
				Quinaspen® 10mg	8	27.59	84.39	7.03	675.12
				Total	**29**	**100.00**	**133.56**	**53.35**	**3 873.19**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	306	55.54	207.19	46.74	63 400.67
				Accuretic® 10/12.5mg	245	44.46	149.12	35.76	36 533.65
				Total	**551**	**100.00**	**181.37**	**51.12**	**99 934.32**
	Generic	Combination	**Quinapril/HCTZ**	Adco-Quinaretic® 20/12.5mg	24	58.54	136.69	26.28	3 280.64
				Adco-Quinaretic® 10/12.5mg	17	41.46	87.39	1.26	1 485.69
				Total	**41**	**100.00**	**116.25**	**31.66**	**4 766.33**
Sep - Dec 2006	Innovator	Single agent	**Quinapril**	Accupril® 10mg	37	40.66	95.48	27.28	3 532.67
				Accupril® 20mg	33	36.26	182.97	81.94	6 037.96
				Accupril® 5mg	16	17.58	30.29	52.16	484.63
				Accupri®l 40mg	5	5.49	186.36	6.68	931.78
				Total	**91**	**99.99**	**120.74**	**80.72**	**10 987.04**
	Generic	Single agent	**Quinapril**	Quinaspen® 20mg	24	72.73	143.31	36.42	3 439.35
				Quinaspen® 10mg	9	27.27	86.19	5.20	775.74
				Total	**33**	**100.00**	**127.73**	**40.34**	**4 215.09**
	Innovator	Combination	**Quinapril/HCTZ**	Accuretic® 20/12.5mg	130	55.79	134.43	50.29	17 475.89
				Accuretic® 10/12.5mg	103	44.21	173.94	69.90	17 915.32
				Total	**233**	**100.00**	**151.89**	**62.78**	**35 391.21**
	Generic	Combination	**Quinapril/HCTZ**	Adco-Quinaretic® 20/12.5mg	217	64.01	131.09	1.94	28 447.16
				Adco-Quinaretic® 10/12.5mg	122	35.99	85.96	6.46	10 487.31
				Total	**339**	**100.00**	**114.85**	**22.09**	**38 934.47**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals

Table B10: Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	**Ramipril**	Tritace® 5mg	8584	37.83	284.66	82.22	2 443 548.44
				Tritace® 2.5mg	7351	32.40	192.13	52.19	1 412 379.40
				Tritace® 10mg	3293	14.51	279.70	46.60	921 049.51
				Ramace® 5mg	1407	6.20	268.51	97.50	377 795.83
				Tritace® 1.25mg	991	4.37	150.29	39.97	148 940.87
				Ramace® 2.5mg	935	4.12	177.22	49.69	165 698.16
				Ramace® 1.25mg	127	0.56	130.06	58.73	16 517.52
				Total	**22688**	**99.99**	**241.80**	**83.00**	**5 485 929.73**
	Innovator	Combination	**Ramipril Felodipine/**	Tri-Plen®	2071	40.97	195.27	33.47	404 403.63
				Tri-Plen Forte®	2984	59.03	314.70	40.52	939 059.30
				Total	**5055**	**100.00**	**265.77**	**69.84**	**404 403.63**
Year 2004	Innovator	Single agent	**Ramipril**	Tritace® 5mg	5406	33.86	278.28	110.71	1 504 368.58
				Tritace® 10mg cap.	4520	28.31	285.44	59.00	1 290 207.88
				Tritace® 2.5mg	4374	27.40	184.75	73.07	808 095.45
				Tritace® 1.25mg	490	3.07	154.79	61.32	75 846.32
				Ramace® 2.5mg cap.	434	2.72	186.87	50.86	81 101.10
				Ramace® 5mg cap.	431	2.70	296.45	88.88	127 770.63
				Ramace® 2.5mg tab.	245	1.53	147.80	39.42	36 210.15
				Ramace® 1.25mg	65	0.41	143.28	48.14	9 312.88
				Tritace® ' Z 1.25mg	1	0.01	82.23	0.00	82.23
				Total	**15966**	**100.01**	**246.34**	**97.27**	**3 932 995.22**
	Generic	Single agent	**Ramipril**	Ramace® 5mg tab.	628	100.00	230.71	88.67	144 886.60
				Total	**628**	**100.00**	**230.71**	**88.67**	**144 886.60**
	Innovator	Combination	**Ramipril/HCTZ**	Tritace® comb. 2.5/5mg	1	100.00	198.13	0.00	198.13
				Total	**1**	**100.00**	**198.13**	**0.00**	**198.13**
	Innovator	Combination	**Ramipril Felodipine/**	Tri-Plen Forte®	3681	62.98	317.73	79.48	1 169 569.31
				Tri-Plen®	2164	37.02	206.73	39.13	447 353.74
				Total	**5845**	**100.00**	**276.63**	**86.13**	**1 616 923.05**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2005	Innovator	Single agent	**Ramipril**	Tritace® 5mg	1845	33.12	230.91	125.70	426 031.68
				Tritace® 10mg	1779	31.93	260.07	101.02	462 655.74
				Tritace® 2.5mg	1550	27.82	170.83	51.11	264 788.70
				Ramace® 2.5mg tab.	212	3.81	146.80	66.55	31 121.58
				Tritace® 1.25mg	171	3.07	140.30	38.77	23 991.45
				Ramace® 2.5mg cap.	10	0.18	174.96	40.59	1 749.57
				Ramace® 5mg cap.	4	0.07	241.20	45.67	964.78
				Total	**5571**	**100.00**	**217.43**	**105.14**	**1 211 303.50**
	Generic	Single agent	**Ramipril**	Ramiwin® 5mg	449	31.2	154.81	67.71	69 510.73
				Ramace® 5mg tab.	419	29.12	209.17	87.85	87 640.68
				Ramiwin® 2.5mg	419	29.12	96.01	26.16	40 229.23
				Ramipril-Hexal® 5mg	84	5.84	143.27	44.18	12 034.32
				Ramipril-Hexal® 2.5mg	39	2.71	89.52	26.76	3 491.24
				Ramiwin® 1.25mg	25	1.74	73.04	20.19	1 826.12
				Ramipril-Hexal® 1.25mg	4	0.28	69.01	6.22	276.04
				Total	**1439**	**100.00**	**149.42**	**78.15**	**215 008.36**
	Innovator	Combination	**Ramipril Felodipine/**	Tri-Plen Forte®	2090	66.82	281.70	57.85	588 750.92
				Tri-Plen®	1038	33.18	187.99	35.65	195 130.55
				Total	**3128**	**100.00**	**250.60**	**67.86**	**783 881.47**

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2006	Innovator	Single agent	**Ramipril**	Tritace® 5mg	405	39.05	225.16	139.42	91 188.36
				Tritace® 10mg cap.	334	32.21	229.86	105.77	76 773.24
				Tritace® 2.5mg	274	26.42	172.73	59.49	47 328.12
				Ramace® 2.5mg tab.	22	2.12	162.02	90.02	3 564.38
				Ramace® 2.5mg cap.	2	0.19	219.17	0.00	438.34
				Total	**1037**	**100.00**	**211.47**	**113.59**	**219 292.44**
	Generic	Single agent	**Ramipril**	Ramiwin® 5mg cap.	697	40.13	175.20	85.47	122 111.27
				Ramiwin® 2.5mg cap.	548	31.55	98.39	24.31	53 920.22
				Ramace® 5mg tab.	126	7.25	235.61	98.07	29 686.50
				Ramipril-Hexal® 5mg	93	5.35	196.22	146.13	18 248.90
				Ran-Ramipril®	81	4.66	230.30	77.80	18 654.65
				Rampil® 2.5mg	53	3.05	112.32	37.38	5 953.19
				Ramipril-Hexal® 2.5mg	45	2.59	99.21	30.29	4 464.47
				Rampil® 10mg	39	2.25	188.47	43.10	7 350.34
				Rampil® 5mg	24	1.38	203.36	69.96	4 880.56
				Ramiwin® 1.25mg cap.	21	1.21	84.98	22.34	1 784.53
				Rampil® 1.25mg	7	0.40	65.80	29.02	460.61
				Austell-Ramipril® 10mg	3	0.17	198.16	100.55	594.48
				Total	**1737**	**100.00**	**154.35**	**87.75**	**268 109.72**
	Innovator	Combination	**Ramipril Felodipine/**	Tri-Plen Forte®	1030	66.54	320.75	68.44	330 373.00
				Tri-Plen®	518	33.46	210.36	41.91	108 966.02
				Total	**1548**	**100.00**	**283.81**	**80.11**	**439 339.02**

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Single agent	**Ramipril**	Tritace® 5mg	1767	33.70	326.22	95.99	576 428.67
				Tritace® 10mg	1413	26.95	323.36	40.88	456 907.00
				Tritace® 2.5mg	1354	25.82	203.70	89.55	275 808.12
				Ramace® 5mg cap.	295	5.63	307.49	90.63	90 708.38
				Ramace® 2.5mg cap.	229	4.37	199.25	52.32	45 627.64
				Tritace® 1.25mg	159	3.03	188.21	70.53	29 925.69
				Ramace® 1.25mg	27	0.51	162.18	26.17	4 378.80
				Total	**5244**	**100.01**	**282.19**	**98.67**	**1 479 784.30**
	Generic	Single agent	**Ramipril**	Ramace® 5mg tab.	76	100.00	307.13	84.50	23 341.64
				Total	**76**	**100.00**	**307.13**	**84.50**	**23 341.64**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen®	691	36.64	244.18	25.43	168 725.94
				Tri-Plen Forte®	1195	63.36	381.61	54.36	456 019.21
				Total	**1886**	**100.00**	**331.25**	**80.60**	**624 745.15**
May - Aug 2004	Innovator	Single agent	**Ramipril**	Tritace® 5mg	1790	34.52	291.60	108.95	521 959.56
				Tritace® 10mg	1464	28.23	293.83	58.33	430 173.47
				Tritace® 2.5mg	1458	28.11	194.48	66.19	283 545.48
				Tritace® 1.25mg	139	2.68	153.95	51.25	21 399.69
				Ramace® 2.5mg cap.	137	2.64	181.04	46.67	24 802.04
				Ramace® 5mg cap.	109	2.10	276.41	81.80	30 128.44
				Ramace® 2.5mg tab.	63	1.21	158.27	37.22	9 970.88
				Ramace® 1.25mg	25	0.48	136.07	58.80	3 401.75
				Tritace ' Z® 1.25mg cap.	1	0.02	82.23	0.00	82.23
				Total	**5186**	**99.99**	**255.58**	**95.50**	**1 325 463.54**
	Generic	Single agent	**Ramipril**	Ramace® 5mg tab.	208	100.00	204.30	110.07	49 981.56
				Total	**208**	**100.00**	**240.30**	**110.07**	**49 981.56**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen Forte®	1178	62.00	315.68	81.27	371 873.19
				Tri-Plen®	722	38.00	203.62	32.38	147 012.00
				Total	**1900**	**100.00**	**273.10**	**86.32**	**518 885.19**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2004	Innovator	Single agent	**Ramipril**	Tritace® 5mg	1849	33.40	219.57	98.66	405 980.35
				Tritace® 10mg	1643	29.68	245.36	46.94	403 127.41
				Tritace® 2.5mg	1562	28.22	159.25	53.57	248 741.85
				Tritace® 1.25mg	192	3.47	127.71	44.12	245 20.94
				Ramace® 2.5mg tab.	182	3.29	144.17	39.60	262 39.27
				Ramace® 2.5mg cap.	68	1.23	156.93	38.41	10 671.42
				Ramace® 5mg cap.	27	0.49	256.81	72.55	6 933.81
				Ramace® 1.25mg	13	0.23	117.87	48.50	1 532.33
				Total	**5536**	**100.01**	**203.71**	**80.07**	**1 127 747.38**
	Generic	Single agent	**Ramipril**	Ramace® 5mg tab.	344	100.00	208.03	60.29	71 563.40
				Total	**344**	**100.00**	**208.03**	**60.29**	**71 563.40**
	Innovator	Combination	**Ramipril/HCTZ**	Tritace® comb. 2.5/5mg	1	100.00	198.13	0.00	198.13
				Total	**1**	**100.00**	**198.13**	**0.00**	**198.13**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen ®	751	36.47	175.25	22.81	131 615.80
				Tri-Plen Forte®	1308	63.53	261.22	47.02	341 676.91
				Total	**2059**	**100.00**	**229.87**	**57.51**	**473 292.71**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Single agent	Ramipril	Tritace® 5mg tab.	718	34.03	233.26	132.60	167 483.74
				Tritace® 2.5mg tab.	642	30.43	181.93	49.78	116 796.78
				Tritace® 10mg cap.	586	27.77	262.90	82.87	154 058.07
				Tritace® 1.25mg tab.	79	3.74	148.57	39.46	11 737.04
				Ramace® 2.5mg tab.	77	3.65	151.92	67.51	11 698.10
				Ramace® 2.5mg cap.	5	0.24	148.29	32.84	741.45
				Ramace® 5mg cap.	3	0.14	231.91	51.11	695.74
				Total	**2110**	**100.00**	**219.53**	**101.23**	**463 210.92**
	Generic	Single agent	Ramipril	Ramace® 5mg tab.	147	75.77	220.52	80.18	32 416.17
				Ramiwin® 2.5mg cap.	29	14.95	99.99	24.38	2 899.63
				Ramiwin® 5mg cap.	17	8.76	152.01	42.04	2 584.09
				Ramiwin® 1.25mg cap.	1	0.52	74.23	0.00	74.23
				Total	**194**	**100.00**	**195.74**	**84.77**	**37 974.12**
	Innovator	Combination	Ramipril/ Felodipine	Tri-Plen Forte®	654	66.13	277.64	60.09	181 579.76
				Tri-Plen®	335	33.87	182.89	27.96	61 269.00
				Total	**989**	**100.00**	**245.55**	**68.29**	**242 848.76**
May - Aug 2005	Innovator	Single agent	Ramipril	Tritace® 5mg tab.	678	33.88	232.90	122.66	157 907.92
				Tritac®e 10mg tab.	635	31.73	263.63	122.33	167 404.82
				Tritace® 2.5mg tab.	548	27.39	166.10	50.16	91 025.34
				Ramace® 2.5mg tab.	79	3.95	146.91	69.65	11 606.23
				Tritace ®1.25mg tab.	60	3.00	135.650.33	37.64	8 139.02
				Ramace® 5mg cap.	1	0.05	269.04	0.00	269.04
				Total	**2001**	**100.00**	**218.07**	**112.40**	**436 352.37**

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May - Aug 2005	Generic	Single agent	Ramipril	Ramiwin® 5mg cap.	145	33.26	159.64	84.06	23 147.68
				Ramiwin® 2.5mg cap.	143	32.8	96.96	31.01	13 865.56
				Ramace® 5mg tab.	132	30.28	203.70	66.68	26 888.77
				Ramipril-Hexal® 5mg tab.	9	2.06	121.64	8.66	1 094.77
				Ramipril-Hexal® 2.5mg tab.	5	1.15	91.95	7.05	459.74
				Ramiwin® 1.25mg cap.	2	0.46	68.61	0.00	137.22
				Total	**436**	**100.01**	**150.44**	**76.88**	**65 593.74**
	Innovator	Combination	Ramipril/ Felodipine	Tri-Plen Forte®	771	67.63	279.82	53.37	215 741.54
				Tri-Plen®	369	32.37	189.82	33.49	70 042.73
				Total	**1140**	**100.00**	**250.69**	**63.74**	**285 784.27**
Sep - Dec 2005	Innovator	Single agent	Ramipril	Tritace® 10mg cap.	558	38.22	253.03	90.87	141 192.85
				Tritace ®5mg tab.	449	30.75	224.14	118.76	100 640.02
				Tritace® 2.5mg tab.	360	24.66	158.24	50.98	56 966.58
				Ramace® 2.5mg tab.	56	3.84	139.59	61.02	7 817.25
				Tritace® 1.25mg tab.	32	2.19	128.61	35.63	4 115.39
				Ramace® 2.5mg cap.	5	0.34	201.62	29.16	1 008.12
				Total	**1460**	**100.00**	**213.52**	**100.23**	**311 740.21**
	Generic	Single agent	Ramipril	Ramiwin® 5mg cap.	287	35.48	152.54	59.22	43 778.96
				Ramiwin® 2.5mg cap.	247	30.53	95.00	23.17	23 464.04
				Ramace® 5mg tab.	140	17.31	202.40	109.80	28 335.74
				Ramipril-Hexal® 5mg tab.	75	9.27	145.86	46.02	10 939.55
				Ramipril-Hexa®l 2.5mg tab.	34	4.20	89.16	28.59	3 031.50
				Ramiwin® 1.25mg cap.	22	2.72	73.39	21.53	1 614.67
				Ramipril-Hexa®l 1.25mg tab.	4	0.49	69.01	6.22	276.04
				Total	**809**	**100.00**	**137.75**	**72.94**	**111 440.50**
	Innovator	Combination	Ramipril/ Felodipine	Tri-Plen Forte®	665	0.67	287.86	60.14	191 429.62
				Tri-Plen ®	334	0.33	191.07	43.54	63 818.82
				Total	**999**	**100.00**	**255.50**	**71.59**	**255 248.44**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan-Apr 2006	Innovator	Single agent	**Ramipril**	Tritace® 5mg tab.	155	37.08	230.66	158.36	35 753.06
				Tritace® 10mg cap.	140	33.49	242.54	115.82	33 954.93
				Tritace® 2.5mg tab.	111	26.56	179.85	57.01	19 962.88
				Ramace® 2.5mg tab.	11	2.63	202.28	109.78	2 225.13
				Ramace® 2.5mg cap.	1	0.24	219.17	0.00	219.17
				Total	**418**	**100.00**	**220.37**	**124.59**	**92 115.17**
	Generic	Single agent	**Ramipril**	Ramiwin® 5mg cap.	195	39.63	182.09	103.98	35 507.21
				Ramiwin® 2.5mg cap.	192	39.02	98.74	24.57	18 958.17
				Ramace® 5mg tab.	51	10.37	216.41	56.53	11 036.73
				Ramipril-Hexal® 5mg tab.	21	4.27	198.14	154.71	4 161.02
				Ran-Ramipril®	14	2.85	224.90	80.44	3 148.58
				Ramipril-Hexal® 2.5mg tab.	11	2.24	90.43	7.48	994.71
				Ramiwin® 1.25mg cap.	4	0.81	78.83	0.01	315.30
				Rampil® 2.5mg	2	0.41	93.58	0.00	187.16
				Rampil ®10mg	1	0.20	183.62	0.00	183.62
				Rampi®l 5mg	1	0.20	277.81	0.00	277.81
				Total	**492**	**100.00**	**151.97**	**91.09**	**74 770.31**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen Forte®	362	66.67	319.44	91.67	115 635.73
				Tri-Plen®	181	33.33	211.78	53.79	38 332.38
				Total	**533**	**100.00**	**306.79**	**39.16**	**163 521.42**

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
May-Aug 2006	Innovator	Single agent	**Ramipril**	Tritace® 5mg tab.	128	39.51	223.32	112.88	28 584.54
				Tritace® 10mg cap.	102	31.48	220.23	115.26	22 463.23
				Tritace®2.5mg tab.	87	26.85	158.86	49.82	13 820.73
				Ramace ®2.5mg tab.	6	1.85	131.86	40.62	791.18
				Ramace® 2.5mg cap.	1	0.31	219.17	0.00	219.17
				Total	**324**	**100.00**	**203.33**	**103.57**	**65 878.85**
	Generic	Single agent	**Ramipril**	Ramiwin® 5mg cap.	252	40.45	168.25	75.20	42 400.25
				Ramiwin® 2.5mg cap.	180	28.89	97.17	23.44	17 491.13
				Ramace® 5mg tab.	40	6.42	227.30	123.29	9 091.92
				Ran-Ramipril®	40	6.42	236.13	79.25	9 445.25
				Ramipril-Hexal® 5mg tab.	35	5.62	195.81	137.26	6 853.27
				Rampi®l 2.5mg	27	4.33	106.85	33.07	2 885.05
				Ramipril-Hexal® 2.5mg tab.	14	2.25	109.35	38.39	1 530.83
				Rampil® 10mg	14	2.25	181.17	9.16	2 536.41
				Rampil® 5mg	11	1.77	215.38	71.73	2 369.13
				Ramiwin® 1.25mg cap.	6	0.96	86.86	33.68	521.14
				Rampi®l 1.25mg	3	0.48	75.97	2.71	227.90
				Austell-Ramipril® 10mg	1	0.16	140.11	0.00	140.11
				Total	**623**	**100.00**	**153.28**	**84.73**	**95 492.39**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen Forte®	350	67.83	321.99	54.93	112 695.64
				Tri-Plen ®	166	32.17	207.18	22.82	34 392.41
				Total	**516**	**100.00**	**285.05**	**71.37**	**147 088.05**

Table B10 (continued): Cost and prevalence of Ramipril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)*	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Sep - Dec 2006	Innovator	Single agent	**Ramipril**	Tritace® 5mg tab.	122	41.36	220.09	139.86	26 850.76
				Tritace® 10mg cap.	92	31.19	221.25	72.63	20 355.08
				Tritace® 2.5mg tab.	76	25.76	178.22	70.28	13 544.51
				Ramace® 2.5mg tab.	5	1.69	273.08	105.58	9 557.85
				Total	**295**	**100.00**	**207.79**	**107.09**	**61 298.42**
	Generic	Single agent	**Ramipril**	Ramiwin® 5mg cap.	250	40.19	176.82	78.79	44 203.81
				Ramiwin® 2.5mg cap.	176	28.3	99.27	24.98	17 470.92
				Ramipril-Hexal® 5mg tab.	37	5.95	195.53	153.21	7 234.61
				Ramace® 5mg tab.	35	5.63	273.08	105.58	9 557.85
				Ran-Ramipril®	27	4.34	224.47	76.58	6 060.82
				Rampil ®10mg	24	3.86	192.93	54.47	4 630.31
				Rampil ®2.5mg	24	3.86	120.04	42.36	2 880.98
				Ramipril-Hexal® 2.5mg tab.	20	3.22	96.95	30.99	1 938.93
				Rampil® 5mg	12	1.93	186.14	67.71	2 233.62
				Ramiwin® 1.25mg cap.	11	1.77	86.19	20.29	948.09
				Rampil® 1.25mg	4	0.64	58.18	38.71	232.71
				Austell-Ramipril® 10mg	2	0.32	227.19	123.14	454.37
				Total	**622**	**100.01**	**157.31**	**88.08**	**97 847.02**
	Innovator	Combination	**Ramipril/ Felodipine**	Tri-Plen Forte®	318	65.03	320.89	48.05	102 041.63
				Tri-Plen®	171	34.97	211.94	41.92	36 241.23
				Total	**489**	**100.00**	**282.79**	**69.40**	**138 282.86**

* The sum of the percentage columns does not amount to 100 due to the fact that the amounts were rounded off to two decimals.

Table B11: Cost and prevalence of Trandolapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Year 2001- 2002	Innovator	Single agent	Trandolapril	Mavik® 2mg	1561	91.45	298.60	138.32	466 119.24
				Mavik® 0.5mg	121	7.09	229.09	75.53	27 719.29
				Gopten® 1mg	25	1.46	239.82	0.00	5 995.50
				Total	**1707**	**100.00**	**292.81**	**135.12**	**499 834.03**
	Innovator	Combination	Trandolapril/ Verapamil	Tarka®	4160	100.00	319.37	63.17	1 328 582.54
				Total	**4160**	**100.00**	**319.37**	**63.17**	**1 328 582.63**
Year 2004	Innovator	Single agent	Trandolapril	Mavik® 2mg	900	94.04	180.83	61.63	162 748.95
				Mavik® 0.5mg	57	5.96	133.90	45.26	7 632.53
				Total	**957**	**100.00**	**178.04**	**61.77**	**170 381.48**
	Innovator	Combination	Trandolapril/ Verapamil	Tarka®	3628	100.00	298.08	66.37	1 081 418.51
				Total	**3628**	**100.00**	**298.08**	**66.37**	**1 081 418.51**
Year 2005	Innovator	Single agent	Trandolapril	Mavik® 2mg	514	88.77	147.80	41.40	75 967.24
				Mavik® 0.5mg	65	11.23	130.07	19.27	8 454.34
				Total	**579**	**100.00**	**145.81**	**39.92**	**84 421.58**
	Innovator	Combination	Trandolapril/ Verapamil	Tarka®	2487	100.00	284.86	45.30	708 434.98
				Total	**2487**	**100.00**	**284.86**	**45.30**	**708 434.98**
Year 2006	Innovator	Single agent	Trandolapril	Mavik® 2mg	233	99.57	159.52	40.77	37 168.89
				Mavik® 0.5mg	1	0.43	84.75	0.00	84.75
				Total	**234**	**100.00**	**159.20**	**40.97**	**37 253.64**
	Innovator	Combination	Trandolapril/ Verapamil	Tarka®	1505	0.00	306.88	40.81	461 857.76
				Total	**1505**	**100.00**	**306.88**	**40.81**	**461 857.76**

Table B11 (continued): Cost and prevalence of Trandolapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2004	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	274	95.47	206.43	58.63	56 562.14
				Mavik® 0.5mg	13	4.53	164.15	16.22	2 133.93
				Total	**287**	**100.00**	**204.52**	**58.05**	**58 696.07**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	993	100.00	337.73	65.35	335 363.97
				Total	**993**	**100.00**	**337.73**	**65.35**	**335 363.97**
May - Aug 2004	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	281	95.25	191.74	67.56	53 878.92
				Mavik® 0.5mg	14	4.75	147.05	32.56	2 058.63
				Total	**295**	**100.00**	**189.62**	**66.96**	**55 937.55**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	1237	100.00	308.48	59.73	381 587.09
				Total	**1237**	**100.00**	**308.48**	**59.73**	**381 587.09**
Sep - Dec 2004	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	345	92.00	151.62	44.82	52 307.89
				Mavik® 0.5mg	30	8.00	114.67	49.96	3 439.97
				Total	**375**	**100.00**	**148.66**	**46.28**	**55 747.86**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	1398	100.00	260.71	51.33	364 467.45
				Total	**1398**	**100.00**	**260.71**	**51.33**	**364 467.45**

Table B11 (continued): Cost and prevalence of Trandolapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2005	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	151	88.82	145.27	43.85	21 936.43
				Mavik® 0.5mg	19	11.18	127.28	4.48	2 418.41
				Total	**170**	**100.00**	**143.26**	**41.73**	**24 354.84**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	827	100.00	284.36	48.15	235 167.79
				Total	**827**	**100.00**	**284.36**	**48.15**	**235 167.79**
May - Aug 2005	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	181	87.86	149.06	42.25	26 980.05
				Mavik® 0.5mg	25	12.14	136.14	26.75	3 403.62
				Total	**206**	**100.00**	**147.49**	**40.85**	**30 383.67**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	881	100.00	282.93	45.81	249 259.89
				Total	**881**	**100.00**	**282.93**	**45.81**	**249 259.89**
Sep - Dec 2005	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	182	89.66	148.63	38.50	27 050.76
				Mavik® 0.5mg	21	10.34	125.35	15.30	2 632.31
				Total	**203**	**100.00**	**146.22**	**37.44**	**29 683.07**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	779	100.00	287.56	41.34	224 007.30
				Total	**779**	**100.00**	**287.56**	**41.34**	**224 007.30**

Table B11 (continued): Cost and prevalence of Trandolapril containing items

Period	Innovator/ Generic	Single/ combination	Active ingredient	Tradename	Frequency (N)	Percent (%)	Average cost/ item (R)	Standard deviation(±)	Total cost (R)
Jan - Apr 2006	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	76	100.00	156.33	36.18	11 881.10
				Total	**76**	**100.00**	**156.33**	**36.18**	**11 881.10**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	533	100.00	306.79	39.16	163 521.42
				Total	**533**	**100.00**	**306.79**	**39.16**	**163 521.42**
May - Aug 2006	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	76	98.70	161.50	43.88	12 274.36
				Mavik® 0.5mg	1	1.30	84.75	0.00	84.75
				Total	**77**	**100.00**	**160.51**	**44.46**	**12 359.11**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	509	100.00	306.13	41.03	155 818.59
				Total	**509**	**100.00**	**306.13**	**41.03**	**155 818.59**
Sep - Dec 2006	Innovator	Single agent	**Trandolapril**	Mavik® 2mg	81	100.00	160.66	42.10	13 013.43
				Total	**81**	**100.00**	**160.66**	**42.10**	**13 013.43**
	Innovator	Combination	**Trandolapril/ Verapamil**	Tarka®	463	100.00	307.81	42.48	142 517.75
				Total	**463**	**100.00**	**307.81**	**42.48**	**142 517.75**

Appendix C

Table C1: ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazepril	**Benazepril**	4	317.03	0.00	1 268.12
	Bisoprolol	23	327.65	115.12	7 535.86
	Doxazosin	1	416.94	0.00	416.94
	Ezetimibe	1	438.95	0.00	438.95
	HCTZ	6	203.83	45.18	1 222.96
	Indapamide	34	253.57	22.54	8 621.3
	Piretanide	1	436.65	0.00	436.65
	Quinapril	3	343.36	0.00	1 030.08
Benazepril/HCTZ	Dihydroergocristine/Clopamide	11	376.08	26.89	4 136.85
	Doxazosin	4	535.50	27.78	2 141.98
	Indapamide	1	425.19	0.00	425.19
	Trandolapril	13	506.05	20.35	6 578.71
	Valsartan	1	551.30	0.00	551.30
Captopril	**Captopril**	25	464.76	89.46	11 619.05
	Captopril/HCTZ	34	307.32	97.59	10 448.85
	Carvedilol	64	365.30	136.23	23 379.13
	Chlorthalidone	8	178.47	30.56	1 427.76
	Dihydroergocristine/Clopamide	50	323.97	33.32	16 198.74
	Doxazosin	35	406.24	109.70	14 218.25
	Enalapril	7	223.91	35.65	1 567.38
	Enalapril/HCTZ	2	339.28	61.95	678.55
	Ezetimibe	55	484.26	203.89	26 634.31
	Furosemide	874	248.61	169.06	217 289.30
	Hydralazine	10	107.87	43.39	1 078.66
	HCTZ/KCl	40	117.54	42.04	4 701.86
	HCTZ/Valsartan	20	306.19	36.02	6 123.89
	HCTZ	170	214.80	150.31	36 464.34

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	HCTZ/Triamterene	86	130.61	92.09	11 232.32
	Indapamide	932	211.75	87.00	197 348.69
	Irbesartan	20	660.52	44.89	13 210.43
	Isosorbide	14	551.92	231.75	7 726.86
	Israpidine	29	421.65	73.26	12 227.82
	Methyldopa	32	200.72	175.58	6 422.93
	Metolazone	6	410.95	38.94	2 465.68
	Metoprolol	1	222.90	0.00	222.90
	Nifedipine	195	400.92	140.11	78 179.48
	Oxprenolol	6	507.02	49.04	3 042.13
	Oxprenolol/Cyclopenthiazide	3	515.35	0.01	1 546.06
	Perindopril	3	247.84	47.25	743.51
	Piretanide	50	209.16	112.96	10 457.88
	Prazosin	26	167.54	28.82	4 355.95
	Ramipril	2	446.65	176.08	893.30
	Reserpine	2	98.32	20.92	196.64
	Sotalol	21	182.80	49.28	3 838.85
	Spironolactone	78	187.79	133.25	14 647.45
	Spironolactone/Isobutylhydrochlorthiazide	3	238.12	80.48	714.37
	Telmisartan/HCTZ	7	383.00	13.10	2 681.00
	Timolol/Amiloride	6	410.60	30.99	2 463.60
	Torazemide	22	243.55	101.68	5 358.07
	Trandolapril/Verapamil	15	437.05	11.30	6 555.81
	Valsartan	12	305.94	6.42	3 671.22

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril/HCTZ	**Captopril/HCTZ**	1	112.32	0.00	112.32
	Carvedilol	18	457.44	89.81	8 233.97
	Dihydroergocristine/Clopamide	2	572.80	0.00	1 145.60
	Doxazosin	13	502.66	104.41	6 534.64
	Ezetimibe	28	399.89	35.19	11 196.86
	Furosemide	19	211.84	72.75	4 024.92
	Indapamide	20	270.45	88.86	5 409.03
	Irbesartan	7	785.59	0.00	5 499.13
	Methyldopa	73	347.24	155.29	25 348.50
	Nifedipine	136	461.28	81.28	62 734.27
	Prazosin	4	234.48	68.81	937.92
	Sotalol	1	206.53	0.00	206.53
	Spironolactone	2	519.67	0.00	1 039.34
	Telmisartan	8	355.60	78.43	2 844.83
Cilazapril	Doxazosin	9	490.67	64.51	4 416.01
	Ezetimibe	6	454.55	41.04	2 727.30
	Furosemide	28	257.39	50.23	7 206.81
	Hydralazine	8	480.75	12.55	3 846.01
	HCTZ	30	206.43	74.18	6 192.84
	HCTZ/Triamterene	3	197.25	0.17	591.74
	Indapamide	83	289.87	66.61	24 059.25
	Israpidine	3	396.47	67.30	1 189.40
	Nifedipine	7	478.16	63.61	3 347.12
	Prazosin	2	260.78	13.33	521.55
	Quinapril/HCTZ	4	354.28	12.20	1 417.12
	Spironolactone	11	249.98	41.24	2 749.74
	Tamsulosin	1	584.43	0.00	584.43
	Timolol/Amiloride	25	732.38	181.71	18 309.56
	Torazemide	7	420.99	106.00	2 946.95

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Cilazapril/HCTZ	Dihydroergocristine/Cl	2	769.86	0.00	1 539.72
	Doxazosin	15	484.83	37.94	7 272.49
	Ezetimibe	45	498.60	38.06	22 437.20
	Furosemide	2	341.22	21.66	682.43
	Indapamide	1	357.87	0.00	357.87
	Irbesartan	5	496.50	10.30	2 482.52
	Israpidine	1	578.12	0.00	578.12
	Nifedipine	96	513.07	60.84	49 254.97
	Torazemide	1	452.97	0.00	452.97
Enalapril	**Enalapril**	101	232.48	77.50	23 480.76
	Enalapril/HCTZ	118	385.80	113.04	45 523.93
	Ezetimibe	126	431.01	108.24	54 306.85
	Felodipine/Ramipril	8	215.92	0.01	1 727.33
	Furosemide	705	301.92	252.66	212 856.33
	Hydralazine	23	349.13	17.63	8 029.95
	HCTZ/KCl	46	135.35	54.36	6 226.28
	HCTZ/Valsartan	7	429.34	105.21	3 005.38
	HCTZ	402	186.56	66.90	74 996.43
	HCTZ/Triamterene	138	199.41	77.12	27 518.20
	Hydroflumethiazide/Reserpine	7	180.96	11.51	1 266.72
	Indapamide	1947	257.21	81.34	500 782.54
	Indapamide/Perindopril	17	371.24	23.00	6 311.07
	Irbesartan	14	386.08	54.25	5 405.18
	Isosorbide	9	466.93	61.92	4 202.33
	Israpidine	113	490.73	120.17	55 452.49
	Labetolol	1	260.61	0.00	560.61
	Lisinopril	2	297.36	8.76	594.71
	Lisinopril/HCTZ	14	444.41	66.22	6 221.69
	Methyldopa	31	371.08	153.61	11 503.60
	Metolazone	6	239.45	51.56	1 436.67

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	Metoprolol	8	273.12	41.14	2 184.96
	Moxonidine	6	390.28	21.74	2 341.69
	Nadolol	4	371.57	48.33	1 486.26
	Nifedipine	310	479.96	104.49	148 786.92
	Nisoldipine	17	576.72	49.63	9 804.24
	Oxprenolol/Cyclopenthiazide	8	554.42	24.79	4 435.38
	Perindopril	11	369.65	22.74	4 066.12
	Piretanide	61	274.75	92.97	16 759.75
	Prazosin	63	345.61	130.67	21 773.4
	Quinapril/HCTZ	7	346.15	170.84	2 423.08
	Reserpine	16	176.68	15.07	2 826.82
	Sotalol	28	260.95	80.78	7 306.72
	Spironolactone	77	217.36	108.45	16 736.78
	Spironolactone/Isobuthylhydrochlorthiaizde	14	354.08	68.58	4 957.09
	Tamsulosin	18	566.33	93.36	10 193.94
	Timolol	1	435.03	0.00	435.03
	Timolol/Amiloride	28	477.81	52.74	13 378.77
	Torazemide	36	345.79	97.04	12 448.31
	Xipamide	1	447.59	0.00	447.59
Enalapril/HCTZ	Ezetimibe	289	494.46	73.60	142 900.38
	Furosemide	111	315.93	107.94	35 068.17
	Hydralazine	4	254.27	5.26	1 017.09
	HCTZ/Valsartan	8	535.60	4.42	4 284.82
	HCTZ	1	329.21	0.00	329.21

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril/HCTZ	Indapamide	152	327.51	63.29	49 781.99
	Indapamide/Perindopril	5	403.35	2.39	2 016.74
	Irbesartan	1	577.85	0.00	577.85
	Israpidine	79	457.32	62.45	36 128.43
	Methyldopa	50	343.85	63.04	17 192.72
	Metolazone	8	560.32	119.70	4 482.55
	Metoprolol	15	745.86	30.18	11 187.88
	Moxonidine	2	491.55	60.29	983.10
	Nifedipine	396	520.37	91.36	206 067.36
	Nisoldipine	10	643.32	179.36	6 433.24
	Oxprenolol	3	504.37	33.26	1 513.11
	Perindopril	14	435.09	65.47	6 091.20
	Piretanide	3	432.84	0.00	1 298.52
	Prazosin	20	343.67	48.95	6 873.42
	Reserpine	9	198.23	1.44	1 784.03
	Sotalol	51	281.13	61.39	14 337.55
	Spironolactone	30	291.03	48.24	8 730.95
	Tamsulosin	3	575.31	7.26	1 725.92
	Telmisartan	9	419.04	16.73	3 771.40
	Terazosin	2	657.49	75.41	1 314.97
	Timolol/Amiloride	11	449.69	15.89	4 946.59
	Torazemide	4	385.71	5.18	1 542.84
	Valsartan	3	434.66	0.00	1 303.98

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Felodipine/Ramipril	Furosemide	47	362.54	92.87	17 039.39
	HCTZ/KCl	2	260.17	58.97	520.34
	HCTZ	34	299.36	68.71	10 178.28
	HCTZ/Triamterene	7	341.60	178.73	2 391.20
	Hydroflumethiazide/Reserpine	2	571.28	267.38	1 142.55
	Indapamide	318	381.41	60.32	121 287.86
	Indapamide/Perindopril	5	457.79	10.18	2 288.95
	Lisinopril	3	375.05	68.48	1 125.16
	Lisinopril/HCTZ	8	581.47	63.31	4 651.74
	Methyldopa	10	435.00	87.83	4 355.49
	Metolazone	2	331.32	88.32	662.64
	Minoxidil	1	675.09	0.00	675.09
	Moxonidine	5	738.95	283.97	3 694.75
	Nifedipine	2	476.98	27.26	953.95
	Perindopril	6	411.83	24.82	2 470.95
	Piretanide	9	443.78	46.15	3 994.05
	Ramipril	3	697.97	139.18	2 093.90
	Reserpine	1	328.81	0.00	328.81
	Sotalol	4	436.26	141.82	1 745.04
	Spironolactone	11	372.07	57.18	4 092.73
	Tamsulosin	3	728.78	8.47	2 186.33
	Telmisartan	1	493.30	0.00	493.30
	Torazemide	17	480.90	133.06	8 175.36
	Valsartan	1	537.87	0.00	537.87

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Fosinopril	**Fosinopril**	1	853.06	0.00	853.06
	Furosemide	89	297.95	110.28	26 517.83
	HCTZ/Valsartan	1	388.55	0.00	388.55
	HCTZ	19	258.27	45.53	4 907.08
	HCTZ/Triamterene	34	218.15	29.63	7 417.16
	Indapamide	255	300.19	56.84	76 548.97
	Irbesartan	4	494.80	30.53	1 979.18
	Nadolol	1	882.74	0.00	882.74
	Nifedipine	10	409.93	33.95	4 099.30
	Nisoldipine	2	654.81	0.00	1 309.62
	Piretanide	10	275.27	29.53	2 752.71
	Spironolactone	12	422.09	128.80	5 065.04
	Tamsulosin	4	511.69	12.08	2 046.77
	Torazemide	2	433.33	57.30	866.66
	Valsartan	2	382.82	7.97	765.63
Fosinopril/HCTZ	Indapamide	1	299.77	0.00	299.77
	Methyldopa	1	646.10	0.00	646.1
	Moxonidine	3	518.76	11.73	1 556.28
	Nifedipine	73	565.59	95.98	41 288.15
	Prazosin	1	290.48	0.00	290.48
	Spironolactone	21	370.68	54.15	7 784.26
	Tamsulosin	4	648.10	7.18	2 592.39

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Indapamide/Perindopril	Indoramin	5	527.52	49.76	2 637.62
	Irbesartan	16	385.70	128.83	6 171.14
	Isosorbide	14	509.22	11.25	7 129.08
	Israpidine	74	585.13	140.17	43 299.72
	Losartan/HCTZ	3	498.89	1.71	1 496.68
	Methyldopa	21	395.40	75.89	8 303.36
	Moxonidine	9	490.01	36.31	4 410.09
	Nifedipine	342	535.28	92.28	183 065.95
	Nisoldipine	8	631.56	16.66	5 052.50
	Perindopril	24	457.62	16.34	10 982.79
	Piretanide	5	322.67	3.14	1 613.35
	Prazosin	5	334.61	43.73	1 673.05
	Quinapril/HCTZ	6	517.94	6.98	3 107.63
	Ramipril	16	453.00	157.45	7 248.07
	Reserpine	13	285.56	11.35	3 712.30
	Sotalol	6	468.58	102.89	2 811.46
	Spironolactone	37	429.94	106.13	15 907.87
	Tamsulosin	17	588.27	100.45	10 000.67
	Telmisartan	18	510.07	16.14	9 181.30
	Timolol/Amiloride	2	819.76	385.49	1 639.52
	Torazemide	11	386.74	20.56	4 254.18
	Trandolapril/Verapamil	10	751.13	163.18	7 511.34

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Lisinopril	**Lisinopril**	30	250.62	100.37	7 518.68
	Lisinopril/HCTZ	8	431.56	82.67	3 452.46
	Methyldopa	26	258.25	38.56	6 714.40
	Methyldopa/Amiloride/HCTZ	10	286.64	8.11	2 866.36
	Metolazone	19	438.83	61.18	8 337.76
	Metoprolol	26	371.93	40.79	9 670.30
	Minoxidil	3	866.41	58.26	2 599.23
	Nadolol	1	334.22	0.00	334.22
	Nifedipine	219	489.76	138.66	107 257.26
	Nisoldipine	9	555.86	42.60	5 002.73
	Piretanide	73	257.65	57.29	18 808.77
	Prazosin	28	436.13	129.70	12 211.74
	Quinapril/HCTZ	6	321.19	0.33	1 927.16
	Sotalol	109	304.13	79.59	33 149.91
	Spironolactone	112	272.66	168.72	30 537.41
	Tamsulosin	11	505.68	67.86	5 562.48
	Telmisartan	1	358.43	0.00	358.43
	Telmisartan/HCTZ	1	447.31	0.00	447.31
	Terazosin	3	398.66	28.84	1 195.97
	Timolol/Amiloride	32	370.69	36.88	11 862.22
	Torazemide	90	365.10	89.46	32 858.93
	Trandolapril/Verapamil	1	835.71	0.00	835.71
	Xipamide	3	374.94	14.81	1 124.81
Lisinopril/HCTZ	**Lisinopril/HCTZ**	1	443.27	0.00	443.27
	Methyldopa	16	465.41	127.23	7 446.63
	Metolazone	1	430.87	0.00	430.87
	Minoxidil	16	496.96	142.51	7 951.28
	Monoxidine	2	567.08	0.00	1 134.16
	Nadolol	2	468.42	22.00	936.83

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Lisinopril/HCTZ	Nifedipine	366	491.56	85.72	179 909.58
	Nisoldipine	74	627.66	73.75	46 447.18
	Perindopril	1	511.21	0.00	511.21
	Piretanide	20	306.35	63.45	6 127.05
	Prazosin	14	484.13	100.00	6 777.87
	Ramipril	24	550.79	31.76	13 219.00
	Sotalol	56	451.44	135.33	25 280.62
	Spironolactone	42	390.15	80.75	16 386.34
	Spironolactone/Isobuthylhydrochlorthiaizde	16	306.07	9.06	4 897.07
	Tamsulosin	3	595.32	157.15	1 785.96
	Telmisartan	2	571.22	10.30	1 142.43
	Terazosin	5	496.28	47.69	2 481.39
	Timolol/Amiloride	1	545.74	0.00	545.74
	Torazemide	5	435.40	88.40	2 177.01
	Trandolapril/Verapamil	17	594.24	16.70	10 102.06
	Valsartan	5	513.26	66.48	2 566.29
Perindopril	Piretanide	28	338.15	23.39	9 468.11
	Prazosin	33	402.84	161.55	13 293.56
	Propranolol/Bendroflomethiaide	7	410.11	1.15	2 870.80
	Quinapril/HCTZ	37	406.76	39.84	15 050.14
	Ramipril	9	366.68	7.57	3 300.15
	Reserpine	31	275.23	65.31	8 532.26
	Sotalol	24	407.99	67.11	9 791.86
	Spironolactone	188	306.30	127.14	57 583.89
	Spironolactone/Isobuthylhydrochlorthiaizde	22	362.98	3.77	7 985.62
	Tamsulosin	14	608.56	122.69	8 519.81
	Telmisartan	48	459.64	35.90	21 918.68
	Terazosin	3	533.40	18.47	1 600.21
	Timolol/Amiloride	33	440.14	42.60	14 524.46
	Torazemide	68	439.39	119.92	29 878.76
	Valsartan	6	452.29	57.66	2 713.73

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Quinapril	**Quinapril**	6	344.74	45.31	2 068.44
	Quinapril/HCTZ	34	496.21	169.09	16 871.26
	Ramipril	2	296.32	34.54	592.63
	Sotalol	8	325.25	6.59	2 602.00
	Spironolactone	46	245.14	92.40	11 276.40
	Spironolactone/Isobutyl	14	413.04	14.71	5 782.58
	Tamsulosin	3	565.49	8.40	1 696.47
	Telmisartan	3	302.47	6.35	907.42
	Terazosin	7	572.67	183.62	4 008.68
	Timolol/Amiloride	1	1156.38	0.00	1 156.38
	Torazemide	55	365.00	51.96	20 075.08
	Trandolapril	18	440.38	21.15	7 926.85
	Valsartan	7	428.95	3.86	3 002.65
Quinapril/HCTZ	**Quinapril/HCTZ**	4	461.39	15.78	1 845.55
	Ramipril	3	279.94	2.50	839.81
	Reserpine	5	229.10	55.04	1 145.48
	Sotalol	10	354.46	37.51	3 544.62
	Spironolactone	44	268.79	88.38	11 826.73
	Tamsulosin	2	593.57	25.98	1 187.14
	Telmisartan	15	500.56	65.88	7 508.47
	Terazosin	3	588.65	147.18	1 765.96
	Torazemide	24	422.45	95.46	10 138.91
	Trandolapril/Verapamil	3	585.53	50.54	1 756.59
	Valsartan	35	482.18	46.55	16 876.25

Table C1 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2001-2002.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Ramipril	**Ramipril**	28	459.72	69.50	12 872.29
	Reserpine	17	538.43	128.88	9 153.23
	Sotalol	28	431.62	88.09	12 085.44
	Spironolactone	122	346.77	141.50	42 306.18
	Spironolactone/Isobutyl	15	386.64	55.95	5 799.54
	Tamsulosin	14	778.06	686.10	10 892.85
	Telmisartan	1	544.52	0.00	544.52
	Terazosin	1	571.59	0.00	571.59
	Timolol/Amiloride	14	556.84	47.97	7 795.74
	Torazemide	67	448.19	123.06	30 028.86
	Trandolapril	3	812.21	45.84	2 436.62
	Valsartan	3	418.40	130.01	1 255.19
Trandolapril	Valsartan	5	564.79	0.00	2 823.95

Table C2: ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Benazepril	Bisoprolol	7	218.38	66.35	1 528.66
	Ezetimibe	8	404.31	24.80	3 234.48
	HCTZ	4	86.74	12.13	346.95
	HCTZ/Triamterene	1	149.57	0.00	149.57
	Indapamide	20	238.85	62.65	4 777.02
Benazepril/HCTZ	Dihydroergocristine/Clopamide	11	473.62	105.62	5 209.79
	Doxazosin	9	570.46	33.09	5 134.10
	Indapamide	1	468.86	0.00	468.86
	Nifedipine	13	683.54	28.59	8 886.07
Captopril	**Captopril**	6	99.67	125.75	598.02
	Captopril/HCTZ	32	115.65	44.80	3 700.79
	Carvedilol	47	205.87	82.84	9 675.75
	Chlorothalidone	4	375.55	0.00	1 502.20
	Dihydroergocristine/Clopamide	1	284.72	0.00	284.72
	Doxazosin	16	318.39	80.00	5 094.26
	Enalapril	1	282.96	0.00	282.96
	Enalapril/HCTZ	5	86.48	7.91	432.38
	Ezetimibe	18	355.93	82.70	6 406.81
	Furosemide	481	189.54	200.83	91 166.64
	Hydralazine	2	68.95	4.91	137.90
	HCTZ/KCl	65	53.68	36.27	3 489.41
	HCTZ	156	81.97	59.38	12 787.88
	HCTZ/Triamterene	85	101.51	55.14	8 628.08
	Hydroflumethiazide/Res	10	117.53	33.22	1 175.34
	Indapamide	686	105.90	66.16	72 650.53
	Indapamide/Perindopril	18	228.46	37.77	41 12.20

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Captopril	Isosorbide	9	305.60	63.64	2 750.41
	Methyldopa	20	112.66	79.63	2 253.23
	Nifedipine	56	379.32	146.12	21 242.08
	Perindopril	8	146.13	13.33	1 169.06
	Prazosin	11	364.04	343.91	4 004.48
	Quinapril/HCTZ	2	257.31	12.59	514.62
	Reserpine	6	73.07	66.68	438.44
	Sotalol	7	173.76	32.78	1 216.30
	Spironolactone	79	131.31	103.24	10 373.38
	Spironolactone/Isobuthylhydrochlorthiaizde	1	154.02	0.00	154.02
	Tamsulosin	3	302.68	0.00	908.04
	Telmisartan	1	246.63	0.00	246.63
	Terazosin	11	299.48	91.61	3 294.25
	Timolol/Amiloride	28	385.04	135.56	10 781.12
	Torazemide	16	249.46	119.97	3 991.43
	Trandolapril	1	148.00	0.00	148.24
Captopril/HCTZ	Carvedilol	16	187.03	52.84	2 992.46
	Dihydroergocristine/Clopamide	3	254.93	17.73	764.78
	Doxazosin	7	990.98	285.76	6 936.85
	Ezetimibe	14	292.92	56.69	4 100.86
	Furosemide	26	175.71	168.20	4 568.37
	HCTZ	4	86.50	10.40	346.01
	Indapamide	23	140.23	63.51	3 225.32
	Methyldopa	5	207.12	136.15	1 035.62
	Nifedipine	52	396.08	147.61	20 596.15
	Prazosin	19	188.71	53.08	3 585.46
	Reserpine	2	162.83	0.01	325.66
	Spironolactone	1	252.09	0.00	252.09

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Cilazapril	Doxazosin	2	529.87	32.82	1 059.73
	Ezetimibe	12	277.33	102.57	3 327.94
	Furosemide	13	261.40	192.30	3 398.26
	HCTZ	19	237.11	73.33	4 505.11
	HCTZ/Triamterene	16	142.49	62.32	2 279.88
	Indapamide	57	222.12	86.25	12 660.67
	Israpidine	8	550.93	90.41	4 407.46
	Nifedipine	10	414.43	55.11	4 144.26
	Prazosin	3	192.85	4.92	578.55
	Quinapril/HCTZ	5	301.72	21.93	1 508.61
	Spironolactone	23	238.30	44.13	5 480.91
	Timolol/Amiloride	4	734.77	96.20	2 939.07
	Torazemide	2	464.88	54.71	929.75
Cilazapril/HCTZ	Doxazosin	10	475.61	91.10	4 756.08
	Ezetimibe	15	454.33	135.74	6 814.95
	Furosemide	7	388.89	75.78	2 722.21
	Indapamide	18	301.16	65.92	5 420.83
	Irbesartan	8	377.71	18.39	3 021.67
	Israpidine	3	384.13	0.00	1 152.39
	Methyldopa	6	206.84	53.10	1 241.05
	Moxonidine	3	549.20	0.00	1 647.60
	Nifedipine	19	444.97	86.62	8 454.46
	Spironolactone	6	324.99	143.02	1 949.96

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril	**Enalapril**	95	139.23	68.30	1 3227.18
	Enalapril/HCTZ	52	155.41	49.37	8 081.08
	Ezetimibe	101	324.33	150.66	32 757.06
	Furosemide	665	169.65	127.90	112 819.61
	Hydralazine	8	213.52	49.83	1 708.19
	HCTZ/KCl	98	70.84	32.05	6 942.45
	HCTZ/Valsartan	37	298.03	51.58	11 027.03
	HCTZ	633	89.20	42.08	56 465.50
	HCTZ/Triamterene	77	85.38	31.14	6 573.98
	Hydroflumethiazide/Reserpine	6	95.10	16.32	570.59
	Indapamide	1917	125.64	58.57	240 848.11
	Indapamide/Perindopril	12	254.99	29.87	3 059.92
	Irbesartan	14	333.51	57.05	4 669.16
	Isosorbide	36	298.03	46.50	10 729.04
	Israpidine	30	350.75	221.05	10 522.61
	Labetalol	2	256.20	0.00	512.40
	Methyldopa	47	240.93	154.54	11 323.52
	Metoprolol	8	329.72	43.34	2 637.79
	Minoxidil	4	396.10	0.00	1 584.40
	Moxonidine	12	278.41	38.65	3 340.90
	Nadolol	1	321.99	0.00	321.99
	Nadolol/Bendroflumethiazide	12	343.97	69.20	4 127.61
	Nebivolol	4	234.46	0.00	937.84
	Nifedipine	238	336.88	100.00	80 177.16
	Perindopril	23	238.13	48.36	5 477.03
	Piretanide	43	170.64	59.53	7 337.52
	Prazosin	27	187.70	71.61	5 067.85
	Quinapril/HCTZ	10	242.81	59.60	2 428.05
	Reserpine	18	88.99	38.74	1 601.85

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril	Sotalol	32	172.26	82.57	5 512.21
	Spironolactone	214	132.90	78.81	28 439.97
	Tamsulosin	34	416.42	81.88	14 158.22
	Telmisartan	13	321.70	41.23	4 182.11
	Telmisartan/HCTZ	4	295.77	134.04	1 183.06
	Terazosin	9	306.80	50.87	2 761.16
	Timolol/Amiloride	18	299.43	79.64	5 389.80
	Torazemide	40	205.90	67.38	8 235.85
	Trandolapril/Verapamil	11	318.38	56.52	3 502.17
	Valsartan	8	262.77	29.69	2 102.13
Enalapril/HCTZ	Ezetimibe	140	376.45	110.95	52 702.90
	Furosemide	104	195.70	104.62	20 352.81
	Hydralazine	16	212.16	92.94	3 394.55
	HCTZ/KCl	11	134.62	41.85	1 480.77
	HCTZ	6	106.48	8.39	638.87
	HCTZ/Triamterene	2	185.97	0.00	371.94
	Indapamide	113	150.28	61.17	16 981.08
	Irbesartan	12	280.48	58.15	3 365.77
	Isosorbide	2	293.91	0.00	587.82
	Israpidine	48	383.43	96.59	18 404.86
	Methyldopa	45	173.92	89.73	7 826.41
	Metoprolol	9	361.58	154.34	3 254.25
	Minoxidil	2	312.34	0.00	624.68
	Moxonidine	20	385.87	104.54	5 717.41
	Nadolol	4	433.35	0.00	1 733.40
	Nebivolol	6	359.71	23.15	2 158.28
	Nifedipine	387	373.32	89.59	144 475.00
	Perindopril	3	249.36	45.29	748.08
	Prazosin	44	195.17	69.14	8 587.49
	Quinapril/HCTZ	2	275.00	0.00	550.00
	Ramipril	1	234.44	0.00	234.44

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
	Reserpine	18	116.91	55.55	2 104.37
	Sotalol	25	238.19	63.25	5 954.78
	Spironolactone	52	136.31	34.29	7 087.97
	Tamsulosin	13	476.69	70.52	6 196.99
	Terazosin	1	507.22	0.00	507.22
	Timolol/Amiloride	12	202.19	88.14	2 426.30
	Torazemide	21	218.51	68.37	4 588.69
	Valsartan	3	454.87	0.00	1 364.64
Felodipine/Ramipril	**Felodipine/Ramipril**	2	411.98	305.68	823.95
	Furosemide	30	381.76	160.38	11 452.89
	HCTZ/Valsartan	42	452.00	140.358221	18 988.49
	HCTZ	72	307.63	67.84	22 149.43
	HCTZ/Triamterene	37	299.66	75.20	11 087.49
	Indapamide	516	348.80	111.62	179 980.17
	Indapamide/Perindopril	16	452.61	111.62	7 241.70
	Irbesartan	7	638.08	30.24	4 466.59
	Lisinopril	1	434.86	0.00	434.86
	Lisinopril/HCTZ	7	552.77	113.05	3 868.98
	Methyldopa	2	473.71	26.38	947.41
	Metoprolol	4	465.93	0.00	1 863.72
	Nebivolol	19	456.85	153.47	8 680.22
	Nifedipine	1	759.16	0.00	759.16
	Perindopril	2	407.60	29.74	815.20
	Piretanide	4	422.97	109.49	1 691.87
	Prazosin	3	345.31	85.59	1 035.92
	Quinapril/HCTZ	2	406.19	56.68	812.38
	Ramipril	2	450.89	38.25	901.77

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Felodipine/Ramipril	Reserpine	1	357.65	0.00	357.65
	Sotalol	1	433.77	0.00	433.77
	Spironolactone	18	333.06	96.50	5 994.99
	Telmisartan	3	423.11	102.04	1 269.34
	Torazemide	2	345.91	71.07	691.81
Fosinopril	Furosemide	32	256.64	53.06	8 212.43
	HCTZ/Valsartan	3	334.86	41.36	1 004.57
	HCTZ	20	211.84	24.23	4 236.73
	HCTZ/Triamterene	15	171.96	29.07	2 579.46
	Indapamide	108	276.87	82.72	29 902.48
	Irbesartan	2	545.81	0.00	1 091.62
	Nifedipine	11	444.89	112.21	4 893.80
	Piretanide	3	355.78	43.65	1 067.34
	Sotalol	8	318.70	41.15	2 549.61
	Spironolactone	17	250.47	55.92	4 258.01
	Tamsulosin	10	597.89	17.82	5 978.90
	Telmisartan/HCTZ	2	559.19	0.00	1 118.38
	Torazemide	2	395.81	159.73	791.61
Fosinopril/HCTZ	Furosemide	30	305.17	62.32	9 155.22
	HCTZ	1	217.87	0.00	217.87
	Indapamide	10	273.64	49.28	2 736.39
	Methyldopa	9	285.72	40.39	2 571.49
	Nifedipine	5	551.61	0.30	2 758.03
	Prazosin	8	327.81	35.84	2 622.47
	Spironolactone	8	247.94	28.06	1 983.52
	Tamsulosin	1	682.85	0.00	682.85

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Indapamide/Perindopril	Irbesartan	52	498.98	77.28	25 947.05
	Isosorbide	14	494.08	102.63	6 917.10
	Israpidine	72	527.31	132.65	37 966.57
	Losartan/HCTZ	6	411.93	24.92	2 471.57
	Methyldopa	80	339.14	141.00	27 131.22
	Moxonidine	25	452.86	57.45	11 321.54
	Nebivolol	26	352.32	61.93	9 160.30
	Nifedipine	749	485.87	84.28	363 915.81
	Perindopril	83	335.57	74.44	27 851.91
	Piretanide	17	295.44	28.66	5 022.53
	Prazosin	33	416.49	177.23	13 744.15
	Quinapril/HCTZ	11	417.37	39.87	4 591.07
	Ramipril	4	536.60	63.25	2 146.38
	Reserpine	16	243.67	41.56	3 898.77
	Sotalol	37	362.13	115.25	13 398.89
	Spironolactone	64	309.28	105.67	19 794.11
	Spironolactone/Isobuthylhydrochlorthiaizde	2	484.07	97.23	968.14
	Tamsulosin	29	599.21	70.84	17 377.11
	Telmisartan	70	466.49	66.54	32 654.30
	Telmisartan/HCTZ	1	523.87	0.00	523.87
	Terazosin	8	1827.69	100.30	14 621.48
	Timolol/Amiloride	6	412.08	168.00	2 472.48
	Torazemide	40	373.68	67.55	14 947.30
	Trandolapril	8	338.97	25.66	2 711.73
	Trandolapril/Verapamil	8	528.53	67.92	4 228.20
	Valsartan	15	460.94	70.63	6 914.13

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Lisinopril	**Lisinopril**	18	134.70	84.63	2 424.56
	Lisinopril/HCTZ	4	208.76	44.20	835.02
	Losartan/HCTZ	7	343.35	42.95	2 403.43
	Methyldopa	20	168.39	68.61	3 367.73
	Metoprolol	20	291.60	138.32	5 831.94
	Moxonidine	1	227.15	0.00	227.15
	Nadolol/Bendriflumethiazide	1	217.73	0.00	217.73
	Nebivolol	13	283.90	38.83	3 690.66
	Nifedipine	82	357.79	86.46	29 339.18
	Perindopril	1	186.88	0.00	186.88
	Piretanide	27	168.44	46.65	4 547.86
	Prazosin	21	208.17	129.65	4 371.62
	Ramipril	1	135.81	0.00	135.81
	Reserpine	4	135.14	43.35	540.55
	Sotalol	42	225.11	102.10	9 454.71
	Spironolactone	129	119.17	54.25	15 373.29
	Spironolactone/Isobuthylhydrochlorthiazide	3	222.34	52.53	667.02
	Tamsulosin	6	533.02	145.12	3 198.09
	Telmisartan	11	295.93	45.63	3 255.21
	Telmisartan/HCTZ	9	287.90	47.09	2 591.12
	Terazosin	13	284.51	60.98	3 698.60
	Timolol/Amiloride	11	165.08	131.82	1 815.83
	Torazemide	56	237.07	77.74	13 275.84

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Lisinopril/HCTZ	Methyldopa	13	295.84	97.87	3 845.91
	Minoxidil	9	491.35	98.83	4 422.12
	Moxonidine	11	523.16	76.86	5 754.81
	Nebivolol	19	445.83	152.21	8 470.80
	Nifedipine	113	477.69	101.21	53 978.52
	Perindopril	6	534.78	18.34	3 208.67
	Piretanide	2	272.80	0.00	545.60
	Reserpine	1	222.04	0.00	222.04
	Sotalol	58	305.82	68.15	17 737.57
	Spironolactone	35	319.60	108.78	11 185.84
	Tamsulosin	2	568.47	14.90	1 136.93
	Telmisartan	3	606.56	12.77	1 819.69
	Terazosin	1	460.77	0.00	460.77
	Torazemide	9	307.73	41.93	2 769.61
	Trandolapril/Verapamil	3	359.96	8.83	1 979.89
	Valsartan	19	530.70	114.06	10 083.21
Moexipril	Nifedipine	2	449.91	45.20	899.82
	Perindopril	2	309.88	56.67	619.75
	Spironolactone	7	407.22	274.78	2 850.54
	Telmisartan/HCTZ	3	451.78	31.96	1 355.35
	Torazemide	3	289.14	0.00	867.42
Perindopril	**Perindopril**	14	323.73	100.72	4 532.20
	Piretanide	17	288.50	73.99	4 904.58
	Prazosin	12	442.64	421.52	5 311.73
	Quinapril	8	340.77	21.46	2 726.16
	Quinapril/HCTZ	24	353.77	63.48	8 490.51
	Ramipril	3	296.52	17.52	889.55
	Reserpine	20	208.41	54.26	4 168.18

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Perindopril	Sotalol	27	243.82	93.07	6 583.11
	Spironolactone	358	224.62	114.00	80 413.89
	Spironolactone/Isobuthylhydrochlorthiaizde	22	307.61	63.53	6 767.51
	Tamsulosin	15	558.24	121.97	8 373.64
	Telmisartan	11	401.80	99.84	4 419.77
	Telmisartan/HCTZ	9	427.27	58.98	3 845.44
	Terazosin	17	585.94	185.31	9 961.01
	Timolol/Amiloride	8	384.66	83.84	3 077.27
	Torazemide	167	315.45	75.35	52 680.31
	Valsartan	8	350.21	18.26	2 801.70
Quinapril	**Quinapril**	7	371.38	60.77	2 599.66
	Quinapril/HCTZ	42	438.82	124.68	18 430.39
	Sotalol	3	293.74	7.96	881.53
	Spironolactone	29	241.23	153.10	6 995.69
	Tamsulosin	6	438.98	131.55	2 633.88
	Terazosin	3	240.51	2.03	721.54
	Timolol/Amiloride	3	531.47	25.53	1 594.41
	Torazemide	17	373.36	144.04	6 347.18
	Valsartan	1	388.10	0.00	388.10
Quinapril/HCTZ	**Quinapril/HCTZ**	12	414.60	92.90	4 975.16
	Ramipril	4	407.14	0.00	1 628.56
	Reserpine	13	235.65	55.93	3 063.48
	Sotalol	37	348.22	176.71	12 884.27
	Spironolactone	22	281.54	76.14	6 193.97
	Tamsulosin	1	441.91	0.00	441.91
	Telmisartan	15	446.62	86.87	6 699.36
	Torazemide	5	356.69	60.02	1 783.47
	Trandolapril/Verapamil	3	541.00	7.97	1 622.99
	Valsartan	12	511.66	453.88	6 139.86

Table C2 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2004.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Ramipril	**Ramipril**	20	451.53	117.52	9 030.55
	Reserpine	4	558.53	78.44	2 234.12
	Sotalol	18	340.25	149.27	6 124.56
	Spironolactone	115	374.79	253.34	43 100.67
	Spironolactone/Isobuthylhydrochlorthiaizde	4	406.46	11.21	1 625.82
	Tamsulosin	15	608.72	92.30	9 130.73
	Terazosin	1	515.17	0.00	515.17
	Timolol/Amiloride	27	516.84	93.23	13 954.56
	Torazemide	62	436.45	108.16	27 060.13
	Trandolapril/Verapamil	20	678.38	198.18	13 567.56
	Valsartan	11	515.64	103.55	5 671.99
Trandolapril/Verapamil	Valsartan	1	500.33	0.00	500.33

Table C3: ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Benazepril	Ezetimibe	12	381.11	0.00	4 573.32
Benazepril/HCTZ	Bisoprolol	1	395.60	0.00	395.60
	Carvedilol	1	444.78	0.00	444.78
	Doxazosin	3	535.67	0.00	1 607.01
	Indapamide	3	320.25	0.00	960.75
	Israpidine	1	467.06	0.00	467.06
	Nifedipine	7	641.00	0.00	4 487.00
Captopril	**Captopril/HCTZ**	18	74.335	1.20	1 338.03
	Carvedilol	13	212.26	100.75	2 759.34
	Doxazosin	8	259.26	33.00	2074.06
	Furosemide	155	157.67	215.33	24 438.10
	Hydralazine	1	25.24	0.00	25.24
	HCTZ/KCl	5	18.62	5.13	93.10
	HCTZ	39	43.18	12.13	1 684.16
	HCTZ/Triamterene	11	79.77	1.19	877.50
	Indapamide	261	67.93	61.35	17 729.45
	Isosorbide	1	300.50	0.00	300.50
	Methyldopa	2	62.61	0.00	125.22
	Nifedipine	21	277.22	23.01	5 821.57
	Perindopril	2	206.38	70.14	412.75
	Prazosin	7	126.37	2.64	884.62
	Quinapril/HCTZ	2	163.13	0.00	326.26
	Reserpine	2	32.24	0.00	64.48
	Spironolactone	28	57.22	37.50	1 602.25
	Timolol/Amiloride	15	265.66	86.48	3 984.92
	Torazemide	12	174.37	78.52	2 092.45
	Trandolapril	1	148.24	0.00	148.24

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Captopril/HCTZ	**Captopril/HCTZ**	1	84.25	0.00	84.25
	Carvedilol	2	150.08	35.15	300.15
	Dihydroergocristine/Clopamide	2	234.46	0.00	468.92
	Doxazosin	9	692.50	148.08	6 232.54
	Furosemide	7	170.43	89.64	1 193.00
	Indapamide	19	96.35	21.51	1 830.65
	Indapamide/Perindopril	7	339.37	0.00	2 375.59
	Irbesartan	4	624.78	162.89	2 499.12
	Methyldopa	2	78.62	0.01	157.23
	Nifedipine	29	301.93	37.40	8 756.09
	Perindopril	3	213.43	31.81	640.29
	Prazosin	13	162.54	101.64	2 113.01
	Reserpine	2	105.22	0.00	210.44
	Spironolactone	3	175.42	51.59	526.25
	Tamsulosin	1	455.60	0.00	455.60
Cilazapril	Furosemide	2	174.78	48.88	349.56
	HCTZ	18	152.46	15.20	2 744.32
	Indapamide	12	160.59	0.00	1 927.08
	Methyldopa	6	184.29	0.00	1 105.74
Cilazapril/HCTZ	Doxazosin	4	424.48	142.06	1 697.90
	Irbesartan	9	376.84	0.00	3 391.56
	Methyldopa	9	182.11	10.38	1 638.95
	Nifedipine	2	427.59	0.00	855.18
	Spironolactone	4	336.75	0.02	1 347.00

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril	**Enalapril**	36	128.51	78.86	4 626.40
	Enalapril/HCTZ	18	136.38	13.52	2 454.83
	Ezetimibe	18	260.09	46.08	4 681.58
	Furosemide	290	120.94	71.83	35 071.18
	Hydralazine	7	124.28	0.00	869.96
	HCTZ/KCl	40	62.49	27.45	2 499.74
	HCTZ/Valsartan	31	283.95	40.30	8 802.57
	HCTZ	412	62.37	21.19	25 697.98
	HCTZ/Triamterene	29	79.08	21.71	2 293.37
	Hydroflumethiazide/Reserpine	2	77.14	0.00	154.28
	Indapamide	828	93.58	38.73	77 484.46
	Indapamide/Perindopril	15	242.07	35.10	3 631.01
	Irbesartan	15	311.36	29.10	4 670.40
	Isosorbide	12	259.80	2.46	3 117.60
	Israpidine	28	358.21	34.66	10 029.93
	Methyldopa	37	155.94	84.48	5 769.93
	Moxonidine	7	228.42	0.95	1 598.97
	Nifedipine	133	289.31	140.85	38 477.93
	Perindopril	6	197.70	0.00	1 186.20
	Piretanide	14	213.23	11.29	2 985.19
	Prazosin	21	149.33	34.97	3 135.95
	Reserpine	1	64.80	0.00	64.80
	Sotalol	14	185.24	48.01	2 593.33
	Spironolactone	105	120.25	51.24	12 625.99
	Tamsulosin	25	342.24	42.00	8 556.03
	Telmisartan	2	328.12	26.47	656.24
	Terazosin	9	301.78	0.01	2 715.99
	Timolol/Amiloride	16	281.72	24.91	4 507.48
	Torazemide	29	198.37	32.71	5 752.77
	Valsartan	12	235.40	0.00	2 824.80

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril/HCTZ	Ezetimibe	38	297.60	51.76	11 308.61
	Furosemide	43	107.89	28.64	4 639.32
	Hydralazine	18	100.25	12.48	1 804.46
	HCTZ/KCl	6	72.70	16.70	436.21
	HCTZ	3	95.11	0.00	285.33
	Indapamide	97	132.89	36.43	12 890.61
	Indapamide/Perindopril	2	169.27	0.00	338.54
	Irbesartan	1	284.68	0.00	284.68
	Israpidine	34	347.86	54.90	11 827.18
	Lercanidipine	3	254.35	10.65	763.05
	Methyldopa	27	158.35	66.82	4 275.53
	Metoprolol	10	150.31	121.53	1 503.09
	Moxonidine	6	297.41	169.61	1 784.47
	Nebivolol	22	354.73	8.29	7 804.00
	Nifedipine	228	309.87	72.00	70 651.08
	Prazosin	23	189.67	42.43	4 362.33
	Ramipril	6	249.55	10.20	1 497.27
	Reserpine	11	90.62	0.87	996.83
	Sotalol	14	147.45	41.14	2 064.36
	Spironolactone	16	112.87	35.68	1 805.85
	Torazemide	3	192.71	74.51	578.14
	Valsartan	4	349.92	4.22	1 399.67
Felodipine/Ramipril	Furosemide	2	287.42	78.62	574.84
	HCTZ/Valsartan	45	422.05	111.92	18 992.47
	HCTZ	25	250.77	38.64	6 269.14
	HCTZ/Triamterene	13	260.14	4.76	3 381.77
	Indapamide	335	290.43	95.76	97 292.39
	Indapamide/Perindopril	17	424.71	0.00	7 220.07
	Irbesartan	7	607.46	8.45	4 552.22

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Felodipine/Ramipril	**Lisinopril**	4	214.09	1.30	856.37
	Lisinopril/HCTZ	4	430.03	38.10	1 720.13
	Moxonidine	2	473.22	252.78	946.44
	Nebivolol	10	269.41	6.80	2 694.11
	Nifedipine	3	609.71	54.71	1 829.12
	Prazosin	10	321.11	0.00	3 211.10
	Sotalol	1	299.16	0.00	299.16
	Spironolactone	7	364.77	92.12	2 553.37
	Tamsulosin	1	713.01	0.00	713.01
	Torazemide	17	390.77	116.07	6 643.10
Fosinopril	Furosemide	1	244.98	0.00	244.98
	HCTZ/Valsartan	7	348.62	27.13	2 440.37
	HCTZ	14	219.76	9.28	3 076.70
	Indapamide	20	268.01	25.78	5 360.13
	Irbesartan	11	381.75	0.00	4 199.25
	Nifedipine	1	411.21	0.00	411.21
	Spironolactone	7	188.11	0.00	1 316.77
	Tamsulosin	7	577.19	0.00	4 040.33
	Torazemide	2	371.22	0.00	742.44
Fosinopril/HCTZ	Furosemide	3	325.23	55.21	975.70
	HCTZ	2	221.26	0.00	442.52
	Irbesartan	1	547.03	0.00	547.03
	Nifedipine	1	412.01	0.00	412.01
	Prazosin	4	265.59	0.00	1 062.36

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Indapamide/Perindopril	Irbesartan	49	495.99	84.46	24 303.71
	Isosorbide	3	393.42	126.16	1 180.27
	Israpidine	132	534.74	86.20	70 585.42
	Lercanidipine	11	334.77	17.50	3 682.52
	Losartan/Hydrochlorthiazide	3	517.31	0.00	1 551.93
	Methyldopa	41	370.09	124.06	15 173.71
	Minoxidil	1	967.50	0.00	967.50
	Moxonidine	22	403.26	32.83	8871.75
	Nadolol	2	346.17	0.00	692.34
	Nifedipine	935	482.15	131.05	450 807.72
	Perindopril	50	293.50	33.11	14 675.02
	Piretanide	9	320.02	60.32	2 880.21
	Prazosin	3	249.43	53.33	748.29
	Quinapril/HCTZ	3	311.50	0.00	934.50
	Ramipril	2	462.65	0.00	925.30
	Reserpine	24	215.66	39.22	5 175.90
	Sotalol	23	392.10	124.13	9 018.35
	Spironolactone	66	267.73	67.87	17 670.24
	Tamsulosin	15	560.25	73.00	8 403.81
	Telmisartan	34	457.30	38.73	15 548.20
	Telmisartan/HCTZ	3	499.08	12.26	1 497.24
	Terazosin	12	800.30	505.58	9 603.54
	Timolol/Amiloride	17	442.63	61.01	7 524.72
	Torazemide	14	363.59	52.69	5 090.24
	Valsartan	1	390.73	0.00	390.73

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Lisinopril	**Lisinopril**	8	91.28	24.98	730.21
	Lisinopril/HCTZ	1	181.00	0.00	181.00
	Losartan/HCTZ	12	301.07	7.26	3 612.89
	Methyldopa	41	138.18	50.68	5 665.48
	Metoprolol	31	207.01	98.89	6 417.30
	Nadolol	9	561.88	10.32	5 056.92
	Nifedipine	49	328.64	42.22	16 103.24
	Perindopril	9	164.53	0.00	1 480.77
	Prazosin	13	150.79	0.00	1 960.27
	Sotalol	18	222.52	77.51	4 005.31
	Spironolactone	40	97.78	36.26	3 911.36
	Spironolactone/Isobuthylhydrochlorthiazide	7	157.93	6.85	1 105.52
	Tamsulosin	3	379.10	81.29	1 137.30
	Telmisartan	11	278.22	74.28	3 060.45
	Telmisartan/HCTZ	6	356.42	12.70	2 138.52
	Terazosin	4	239.63	1.63	958.50
	Torazemide	4	161.65	49.04	646.60
Lisinopril/HCTZ	**Lisinopril/HCTZ**	2	333.34	0.00	666.68
	Methyldopa	26	259.37	60.33	6 743.52
	Nifedipine	41	408.04	59.58	16 729.80
	Prazosin	1	113.78	0.00	113.78
	Sotalol	8	298.98	71.46	2 391.84
	Tamsulosin	1	313.31	0.00	313.31
	Terazosin	1	413.50	0.00	413.50
	Torazemide	3	265.22	0.00	795.66
	Valsartan	3	310.38	0.00	931.14
Moexipril	Nifedipine	18	394.33	40.95	7 097.90
	Spironolactone	2	200.07	24.83	400.13

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Perindopril	**Perindopril**	2	157.81	0.00	315.62
	Piretanide	16	256.32	68.26	4 101.16
	Prazosin	13	239.43	59.42	3 112.63
	Quinapril	2	323.42	64.23	646.84
	Quinapril/HCTZ	3	311.26	89.54	933.77
	Ramipril	1	286.42	0.00	286.42
	Reserpine	11	166.21	13.96	1 828.33
	Sotalol	12	309.54	74.17	3 714.48
	Spironolactone	271	212.41	124.05	57 562.11
	Spironolactone/Isobutylhydrochlorthiaizde	23	266.43	32.22	6 127.95
	Tamsulosin	15	513.78	46.66	7 706.63
	Telmisartan/HCTZ	10	405.64	36.59	4 056.40
	Terazosin	18	426.63	194.94	7 679.33
	Timolol/Amiloride	10	537.52	0.00	5 375.20
	Torazemide	138	288.02	42.75	39 747.27
	Valsartan	11	382.91	43.59	4 212.04
Quinapril	**Quinapril**	6	321.25	0.00	1 927.50
	Quinapril/HCTZ	11	235.50	28.41	2 590.55
	Spironolactone	22	246.94	21.88	5 432.59
	Tamsulosin	4	421.94	3.66	1 687.77
	Telmisartan	1	427.23	0.00	427.23
	Torazemide	12	279.48	0.00	3 353.76
Quinapril/HCTZ	**Quinapril/HCTZ**	1	381.61	0.00	381.61
	Reserpine	4	227.31	42.24	909.23
	Sotalol	11	219.21	16.15	2 411.29
	Spironolactone	1	247.06	0.00	247.06
	Torazemide	7	264.31	0.00	1 850.17

Table C3 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2005.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Ramipril	**Ramipril**	5	286.99	86.32	1 434.95
	Sotalol	29	273.27	49.32	7 924.83
	Spironolactone	33	245.33	163.56	8 095.97
	Spironolactone/Isobutylhydrochlorthiaizde	9	395.87	67.53	3 562.86
	Tamsulosin	33	536.43	88.26	17 702.20
	Telmisartan/HCTZ	6	577.66	0.00	3 465.96
	Timolol/Amiloride	26	427.78	41.20	11 122.32
	Torazemide	68	361.36	101.43	24 572.22
Trandolapril/Verapamil	Valsartan	3	676.85	166.71	2 030.56

Table C4: ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Benazperil	Ezetimibe	2	381.11	0.00	762.22
Benazperil/HCTZ	Carvedilol	2	380.88	0.04	761.75
	Indapamide	5	321.53	1.71	1 607.64
	Nifedipine	11	648.50	12.85	7 133.53
Captopril	Carvedilol	1	209.83	0.00	209.83
	Doxazosin	2	288.42	0.00	576.84
	Furosemide	16	231.22	180.58	3 699.57
	HCTZ/KCl	1	9.55	0.00	9.55
	HCTZ	19	35.32	14.54	671.10
	HCTZ/Triamterene	3	105.27	22.69	315.81
	Indapamide	63	79.74	96.64	5 023.34
	Indapamide/Perindopril	2	207.79	31.90	415.58
	Lisinopril/HCTZ	1	68.46	0.00	68.46
	Methyldopa	1	351.78	0.00	351.78
	Nifedipine	10	254.25	10.74	2 542.48
	Prazosin	1	81.73	0.00	81.73
	Quinapril/HCTZ	5	195.38	44.84	976.88
	Spironolactone	21	40.40	13.44	848.50
	Torazemide	1	174.92	0.00	174.92
Quinapril/HCTZ	Carvedilol	3	157.15	21.35	471.46
	Doxazosin	5	657.25	69.66	3 286.24
	Enalapril	1	161.23	0.00	161.23
	Furosemide	3	178.53	22.05	535.59
	Indapamide	9	186.24	261.07	1 676.16
	Indapamide/Perindopril	16	294.41	42.36	4 710.58
	Irbesartan	1	1146.81	0.00	1 146.81
	Lercanidipine	2	303.35	0.00	606.70

Table C4 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Quinapril/HCTZ	**Perindopril**	1	236.14	0.00	236.14
	Prazosin	1	153.93	0.00	153.93
	Reserpine	1	104.31	0.00	104.31
	Spironolactone	2	213.99	165.12	427.98
	Tamsulosin	4	469.64	0.05	1 878.54
	Telmisartan	1	332.26	0.00	332.26
Cilazapril	HCTZ	9	181.30	7.01	1 631.69
	Torazemide	1	309.20	0.00	309.20
Cilazapril/HCTZ	Nifedipine	1	349.00	0.00	349.00
	Enalapril	9	135.95	64.47	1 223.57
	Enalapril/HCTZ	9	141.81	11.43	1 276.31
	Ezetimibe	2	341.61	161.04	683.21
	Furosemide	31	127.92	103.90	3 965.52
	HCTZ/KCl	12	75.05	13.75	900.58
	HCTZ/Valsartan	17	325.40	17.53	5 531.88
	HCTZ	32	65.59	22.92	2 098.94
	Indapamide	312	99.35	39.41	30 996.32
	Indapamide/Perindopril	1	264.07	0.00	264.07
	Israpidine	21	361.21	26.18	7 585.41
	Methyldopa	10	248.83	98.58	2 488.26
	Nifedipine	67	325.96	65.09	21 839.04
	Perindopril	5	235.60	0.00	1 178.00
	Prazosin	10	175.33	92.30	1 753.27
	Reserpine	1	93.36	0.00	93.36
	Sotalol	3	233.06	73.20	699.18
	Spironolactone	39	98.46	44.66	3 839.96
	Tamsulosin	14	389.31	54.98	5 450.37
	Torazemide	16	248.92	4.24	3 982.73
	Valsartan	1	320.41	0.00	320.41

Table C4 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril/HCTZ	Ezetimibe	10	318.05	6.23	3 180.54
	Furosemide	13	167.90	32.90	2 182.64
	Indapamide	16	141.70	37.67	2 267.14
	Isosorbide	5	374.62	0.00	1 873.10
	Israpidine	25	380.03	49.79	9 500.67
	Lercanidipine	2	266.88	0.00	533.76
	Methyldopa	2	197.50	0.00	395.00
	Metoprolol	15	218.49	157.46	3 277.30
	Moxonidine	3	264.13	0.00	792.39
	Nebivolol	12	351.34	4.95	4 216.06
	Nifedipine	139	350.45	51.72	48 713.12
	Prazosin	16	190.33	39.98	3 045.21
	Spironolactone	1	184.07	0.00	184.07
	Tamsulosin	1	470.39	0.00	470.39
	Valsartan	10	346.77	1.64	3 467.72
Felodipine/Ramipril	HCTZ/Valsartan	21	489.26	146.40	10 274.41
	HCTZ	7	304.51	0.00	2 131.57
	Indapamide	160	337.54	93.28	54 006.77
	Indapamide/Perindopril	1	557.95	0.00	557.95
	Spironolactone	3	307.04	84.39	921.11
	Tamsulosin	9	531.91	136.40	4 787.16
	Torazemide	1	656.86	0.00	656.86
Fosinopril	HCTZ	1	12.48	0.00	12.48
	Tamsulosin	5	577.19	0.00	2 885.95

Table C4 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Indapamide/Perindopril	**Indapamide/Perindopril**	3	501.29	198.64	1 503.86
	Irbesartan	27	487.95	21.38	13 174.66
	Isosorbide	3	487.32	25.97	1 461.95
	Israpidine	102	516.09	108.64	52 640.68
	Lercanidipine	16	384.98	71.03	6 159.65
	Lisinopril/HCTZ	3	302.14	0.00	906.72
	Methyldopa	36	305.35	79.33	10 992.44
	Metoprolol	9	632.53	193.05	5 692.80
	Moxonidine	9	566.78	201.38	5 101.00
	Nifedipine	950	489.18	72.65	464 720.03
	Perindopril	22	267.27	87.02	5 879.98
	Prazosin	7	234.50	20.73	1 641.47
	Quinapril/HCTZ	5	365.81	28.66	1 829.05
	Ramipril	8	578.05	514.95	4 624.39
	Reserpine	5	210.76	20.84	1 053.80
	Sotalol	21	395.41	105.01	8 303.52
	Spironolactone	47	275.06	107.67	12 927.93
	Tamsulosin	34	588.75	24.82	20 017.44
	Telmisartan	22	470.60	25.56	10 353.20
	Telmisartan/HCTZ	4	454.66	27.12	1 818.65
	Terazosin	1	331.14	0.00	331.14
	Timolol/Amiloride	6	474.35	18.12	2 846.12
	Torazemide	26	388.62	77.27	10 104.07
	Trandolapril/Verapamil	5	525.84	0.00	2 629.20
	Valsartan	1	443.14	0.00	443.14

Table C4 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Lisinopril	**Lisinopril**	1	249.83	0.00	249.83
	Metoprolol	6	209.60	141.58	1 257.60
	Nifedipine	5	287.54	27.70	1 437.68
	Spironolactone	5	68.75	11.84	343.77
	Telmisartan/HCTZ	11	333.81	13.83	3 671.92
	Terazosin	6	323.64	63.05	1 941.84
Lisinopril/HCTZ	Nifedipine	65	417.61	73.05	27 144.72
	Perindopril	19	357.79	63.03	6 798.04
	Spironolactone	1	348.47	0.00	348.47
	Tamsulosin	1	450.54	0.00	450.54
Moexipril	Nifedipine	8	414.81	64.06	3 318.50
	Telmisartan	1	461.13	0.00	461.13
	Telmisartan/HCTZ	10	434.51	39.51	4 345.10
Perindopril	Piretanide	1	248.33	0.00	248.33
	Prazosin	8	213.50	34.58	1 707.98
	Quinapril/HCTZ	2	371.18	0.00	742.36
	Quinapril/HCTZ	13	443.30	61.15	5 762.93
	Reserpine	15	175.21	1.04	2 628.09
	Sotalol	6	492.30	246.66	2 953.81
	Spironolactone	170	213.34	91.17	36 268.25
	Spironolactone/Isobutylhydrochlorthiaizde	11	296.46	0.00	3 261.06
	Tamsulosin	34	512.98	42.70	17 441.46
	Telmisartan	2	482.30	87.21	964.59
	Telmisartan/HCTZ	4	426.55	15.28	1 706.18
	Terazosin	8	608.13	0.12	4 865.02
	Torazemide	50	310.98	41.22	15 549.21
	Valsartan	11	425.96	82.20	1 684.52

Table C4 (continued): ACE inhibitor prescribed together with one other antihypertensive item for 2006.

Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Quinapril	Spironolactone	12	185.76	64.33	2 229.07
	Telmisartan	3	400.65	46.04	1 201.95
	Torazemide	2	315.13	28.53	630.25
Quinapril/HCTZ	Sotalol	3	152.52	0.00	457.56
Quinapril/HCTZ	Sotalol	8	292.31	211.46	2 338.48
	Tamsulosin	1	717.90	0.00	717.90
Ramipril	**Ramipril**	11	361.50	196.97	3 976.49
	Sotalol	2	165.42	0.18	330.84
	Spironolactone	27	162.65	98.63	4 391.51
	Tamsulosin	36	488.09	26.16	17 571.28
	Telmisartan/HCTZ	5	480.83	66.73	2 404.14
	Torazemide	11	314.64	0.00	3 461.04
Trandolapril/Verapamil	Valsartan	2	570.69	0.00	1 141.38

Table C5: ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazepril	Bumetanide/KCL	Nifedipine	1	660.27	0.00	660.27
	Carvedilol	Furosemide	3	571.45	0.00	1 714.35
		Indapamide	1	432.54	0.00	432.54
	Furosemide	Telmisartan	1	472.48	0.00	472.48
	HCTZ/Triamterene	Israpidine	2	647.88	2.18	1 295.75
	Nifedipine	Prazosin	1	584.50	0.00	584.50
Captopril	**Captopril/HCTZ**	Dihydroergocristine/Clopamide	12	558.46	9.21	6 701.51
		Indapamide	6	752.79	0.00	4 516.74
	Carvedilol	Carvedilol	1	516.15	0.00	516.15
		Ezetimibe	3	746.85	0.00	2 240.55
		Furosemide	62	512.57	200.40	31 779.27
		HCTZ/KCl	1	253.96	0.00	253.96
		Indapamide	1	357.4	0.00	357.40
		Spironolactone	9	517.98	157.17	4 661.78
		Torazemide	2	442.26	120.83	884.52
	Dihydroergocristine/Clopamide	Methyldopa	19	662.04	163.15	12 578.77
		Nifedipine	2	689.42	0.00	1 378.84
	Doxazosin	Furosemide	5	743.95	50.68	3 719.77
		Moxonidine	2	828.17	0.00	1 656.34
		Oxprenolol/Cyclopenthiazide	2	650.07	146.07	1 300.89
		Telmisartan	11	567.17	31.77	6 238.88
	Enalapril/HCTZ	Nifedipine	1	738.72	0.00	738.72
	Ezetimibe	Furosemide	15	481.73	1.46	7 226.01
		Indapamide	10	432.23	18.31	4 322.34
		Spironolactone	2	546.49	0.00	1 092.98

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Furosemide	Furosemide	11	860.91	478.42	9 469.96
		HCTZ/KCl	2	375.99	418.06	751.97
		Indapamide	11	280.92	54.58	3 090.07
		Indoramin	6	596.83	11.02	3 580.98
		Isosorbide	1	987.20	0.00	987.20
		Israpidine	1	459.47	0.00	459.47
		Methyldopa	34	366.80	39.29	12 471.35
		Nifedipine	5	507.40	105.44	2 536.99
		Prazosin	2	722.94	779.97	1 445.88
		Spironolactone	199	369.47	262.30	73 524.43
		Timolol/Amiloride	2	491.61	0.00	983.22
	HCTZ/KCl	Nifedipine	1	327.58	0.00	327.58
	HCTZ	Israpidine	13	557.26	189.06	7 244.41
		Nifedipine	2	321.00	36.66	642.00
		Prazosin	3	202.39	79.86	607.16
		Spironolactone	5	186.44	34.88	932.22
		Timolol/Amiloride	1	399.53	0.00	399.53
	HCTZ/Triamterene	Minoxidil	1	940.97	0.00	940.97
		Nifedipine	11	559.38	107.93	6 153.22
	Hydroflumethiazide/Res	Indapamide	1	260.27	0.00	260.27
	Indapamide	Israpidine	30	501.63	85.71	15 048.94
		Methyldopa	11	357.33	213.73	3 930.64
		Moxonidine	1	560.20	0.00	560.20
		Nifedipine	20	527.38	93.00	10 547.69
		Perindopril	14	551.86	146.96	7 726.03
		Piretanide	2	303.72	67.64	607.44
		Telmisartan	1	424.37	0.00	424.37

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Isosorbide	Spironolactone	8	860.28	9.72	6 882.22
	Israpidine	Nifedipine	1	613.44	0.00	613.44
		Spironolactone	3	520.92	24.79	1 562.77
	Methyldopa	**Perindopril**	2	348.57	0.00	697.14
	Metolazone	Spironolactone	1	205.91	0.00	205.91
		Torazemide	3	1197.07	0.00	3 591.21
	Nifedipine	Prazosin	23	656.36	77.04	15 096.23
		Spironolactone	2	512.19	86.66	1 024.38
	Piretanide	Spironolactone	5	260.14	17.66	1 300.70
Captopril/HCTZ	Carvedilol	Spironolactone	1	909.72	0.00	909.72
	Ezetimibe	Methyldopa	5	568.79	12.58	2 843.94
	Furosemide	Metolazone	1	365.09	0.00	365.09
	Methyldopa	Nifedipine	4	424.97	5.18	1 699.89
	Nifedipine	**Perindopril**	1	717.64	0.00	717.64
Cilazapril	Doxazosin	Spironolactone	5	669.02	47.47	3 345.09
	Ezetimibe	Furosemide	4	403.65	15.60	1 614.60
	Indapamide	Nifedipine	1	532.36	0.00	532.36
	Israpidine	Spironolactone	19	496.31	14.29	9 429.95
Cilazapril/HCTZ	Dihydroergocristine/Clopamide	Minoxidil	3	1081.40	23.46	3 244.21
	Furosemide	HCTZ/Valsartan	5	472.59	21.54	2 362.97
Enalapril	Enalapril	Ezetimibe	5	530.16	10.79	2 650.82
		Furosemide	23	462.25	120.64	10 631.66
		HCTZ/Triamterene	8	200.62	29.65	1 604.96
		Methyldopa	1	451.88	0.00	451.88
		Nisoldipine	6	579.75	61.37	3 478.50
		Xipamide	3	463.93	0.00	1 391.79

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	**Enalapril/HCTZ**	Ezetimibe	2	522.69	0.00	1 045.38
		HCTZ/Triamterene	1	514.11	0.00	514.11
		Prazosin	2	387.78	0.00	775.56
		Sotalol	25	495.45	127.01	12 386.34
	Ezetimibe	Furosemide	9	617.82	77.75	5 560.35
		HCTZ	6	559.11	7.82	3 354.66
		Indapamide	6	562.46	8.63	3 374.75
		Nadolol/Bendroflumethiazide	7	789.18	20.09	5 524.25
		Spironolactone	2	476.98	17.01	953.96
		Terazosin	1	759.98	0.00	759.98
	Furosemide	Furosemide	2	548.65	527.35	1 097.29
		HCTZ/Triamterene	2	138.53	0.06	277.05
		Indapamide	34	372.09	81.65	12 650.89
		Israpidine	2	358.90	8.35	717.79
		Methyldopa	2	725.04	466.52	1 450.08
		Metolazone	11	848.48	715.30	9 333.23
		Nifedipine	35	865.78	371.63	30 302.14
		Perindopril	1	760.31	0.00	760.31
		Prazosin	19	615.44	55.13	11 693.45
		Quinapril/HCTZ	9	396.47	15.83	3 568.26
		Ramipril	1	404.56	0.00	404.56
		Reserpine	1	246.55	0.00	246.55
		Spironolactone	72	430.20	264.32	30 974.25
	HCTZ/KCl	Indapamide	1	177.91	0.00	177.91
	HCTZ	Methyldopa	5	348.93	2.93	1 744.66
		Nadolol	8	465.81	2.38	3 726.51
		Prazosin	1	608.42	0.00	608.42
		Reserpine	5	132.95	24.66	664.75
		Sotalol	1	203.16	0.00	203.16
		Timolol	5	472.67	0.00	2 363.35

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard deviation (±)	Total cost (R)
Enalapril	HCTZ/Triamterene	Isosorbide	9	592.73	3.93	5 334.56
		Israpidine	3	409.32	3.35	1 227.95
		Labetolol	1	640.21	0.00	640.21
		Metoprolol	9	437.52	5.34	3 937.66
		Nifedipine	2	726.25	0.00	1 452.50
		Quinapril/HCTZ	5	367.99	1.47	1 839.93
	Indapamide	Israpidine	13	599.61	24.41	7 794.90
		Methyldopa	5	401.48	165.19	2 007.41
		Moxonidine	11	578.62	19.63	6 364.85
		Nifedipine	78	546.76	88.38	42 647.43
		Perindopril	1	397.68	0.00	397.68
		Piretanide	2	454.25	0.00	908.50
		Prazosin	4	297.42	45.04	1 189.67
		Sotalol	5	322.52	38.53	1 612.60
	Isosorbide	Spironolactone	1	393.75	0.00	393.75
	Methyldopa	Spironolactone	1	423.83	0.00	423.83
	Nifedipine	**Perindopril**	2	669.93	8.70	1 339.86
		Prazosin	5	834.89	13.89	4 174.43
		Telmisartan	10	843.45	24.58	8 434.47
		Torazemide	11	602.09	53.66	6 622.97
	Prazosin	Reserpine	1	1640.11	0.00	1 640.11
		Spironolactone	3	703.83	218.18	2 111.48
	Spironolactone	Torazemide	1	161.85	0.00	161.85
		Valsartan	2	394.24	0.00	788.48

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril/HCTZ	Ezetimibe	Indapamide	2	537.62	17.01	1 075.23
		Terazosin	3	957.97	0.00	2 873.91
	Furosemide	Indapamide	1	474.45	0.00	474.45
		Metolazone	1	669.12	0.00	669.12
		Nifedipine	13	800.06	97.17	10 400.73
		Spironolactone	4	1032.43	71.72	4 129.71
	Hydralazine	Nifedipine	1	701.31	0.00	701.31
	HCTZ/Triamterene	Valsartan	13	535.50	54.68	6 961.48
	Indapamide	Nifedipine	13	697.30	26.45	9 064.95
	Israpidine	Sotalol	20	790.73	41.32	15 814.66
	Methyldopa	Nifedipine	4	549.54	53.73	2 198.14
	Minoxidil	Nifedipine	5	569.88	0.94	2 849.38
	Nifedipine	Piretanide	3	500.27	42.21	1 500.82
		Prazosin	7	707.35	17.48	4 951.47
		Spironolactone	2	465.23	0.00	930.46
		Valsartan	3	913.07	13.11	2 739.20
	Sotalol	Sotalol	4	461.10	46.65	1 844.39
Felodipine/Ramipril	**Felodipine/Ramipril**	Indapamide	1	610.11	0.00	610.11
	Furosemide	Methyldopa	2	429.21	0.05	858.41
		Spironolactone	2	1012.95	0.00	2 025.90
	HCTZ	Reserpine	3	383.72	15.27	1 151.17
	Indapamide	Irbesartan	3	649.39	0.00	1 948.17
		Methyldopa	3	516.29	0.00	1 548.87
		Prazosin	2	509.03	61.57	1 018.05
		Trandolapril/Verapamil	1	723.01	0.00	723.01
	Losartan/HCTZ	Minoxidil	5	897.71	18.14	4 488.53
	Moxonidine	Valsartan	4	813.24	54.64	3 252.94
	Spironolactone	Torazemide	1	472.94	0.00	472.94

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Fosinopril	HCTZ	Nifedipine	2	693.37	310.63	1 386.74
		Sotalol	2	707.78	3.10	1 415.55
Fosinopril/HCTZ	Methyldopa	Prazosin	3	815.76	87.74	2 447.27
Indapamide/Perindopril	Isosorbide	Nifedipine	5	863.97	11.55	4 319.83
	Israpidine	Methyldopa	1	975.96	0.00	975.96
	Lisinopril	Methyldopa	2	460.00	220.41	920.00
	Methyldopa	Methyldopa	1	567.75	0.00	567.75
		Nifedipine	1	839.92	0.00	839.92
		Perindopril	1	599.80	0.00	599.80
	Minoxidil	Nifedipine	2	1037.89	0.00	2 075.78
	Moxonidine	**Trandolapril/Verapamil**	2	831.02	0.00	1 662.04
	Nifedipine	Nifedipine	3	852.10	2.52	2 556.31
		Prazosin	3	689.76	293.55	2 069.27
		Sotalol	6	648.31	67.08	3 889.83
		Spironolactone	1	832.46	0.00	832.46
		Torazemide	1	734.67	0.00	734.67
	Quinapril/HCTZ	Torazemide	5	552.48	15.00	2 762.41
	Spironolactone	Torazemide	3	570.95	28.47	1 712.84
Lisinopril	Methyldopa	Nifedipine	2	705.45	67.80	1 410.89
	Nifedipine	Spironolactone	6	382.20	7.31	2 293.20
		Telmisartan	15	673.52	35.13	10 102.74
	Piretanide	Spironolactone	2	210.20	0.00	420.40
	Spironolactone	Torazemide	4	382.09	106.86	1 528.36
Lisinopril/HCTZ	Metolazone	Nifedipine	1	1548.04	0.00	1 548.04
	Sotalol	Spironolactone	1	681.01	0.00	681.01
	Terazosin	Terazosin	1	923.68	0.00	923.68
Perindopril	Sotalol	Torazemide	2	638.59	0.00	1 277.18
	Spironolactone	Tamsulosin	1	166.47	0.00	166.47
		Terazosin	2	565.40	16.40	1 130.79
		Torazemide	41	478.69	156.28	19 626.16

Table C5 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Ramipril	Spironolactone	Tamsulosin	2	658.37	0.00	1 316.74
		Torazemide	44	603.41	288.41	26 549.84

Table C6: ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazepril	Indapamide	Nifedipine	1	227.41	0.00	227.41
Captopril	**Captopril**	Furosemide	1	320.02	0.00	320.02
		HCTZ/Triamterene	5	77.74	4.22	388.72
	Carvedilol	Doxazosin	1	185.85	0.00	185.85
		Ezetimibe	3	639.34	173.07	1 918.02
		Furosemide	48	274.62	136.19	13 181.92
		HCTZ/Triamterene	5	180.99	22.00	904.95
		Spironolactone	10	159.934	62.06	1 599.34
		Torazemide	6	433.62	14.06	2 601.74
	Dihydroergocristine/Clopamide	Furosemide	2	364.495	126.48	728.99
		Indapamide	14	308.22	90.88	4 315.04
		Israpidine	2	328.76	214.83	657.51
		Methyldopa	8	303.14	33.12	2 425.09
	Doxazosin	Furosemide	3	724.81	189.97	2 174.44
		HCTZ	17	277.01	127.23	4 709.10
	Ezetimibe	Ezetimibe	1	291.14	0.00	291.14
		Furosemide	5	359.80	137.22	1 798.98
		HCTZ/KCl	2	164.93	139.69	329.85
		HCTZ	1	88.10	0.00	88.10
		Indapamide	12	322.68	105.16	3 872.21

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Furosemide	Furosemide	1	218.02	0.00	218.02
		Hydralazine	3	400.37	162.90	1 201.12
		HCTZ/KCl	8	78.50	48.90	628.00
		HCTZ	4	151.46	157.29	605.85
		Indapamide	2	178.01	21.65	356.02
		Isosorbide	11	348.13	73.45	3 829.45
		Methyldopa	2	132.36	9.67	264.71
		Nifedipine	18	548.63	275.21	9 875.39
		Perindopril	4	242.30	35.42	969.19
		Spironolactone	133	286.38	206.05	38 088.18
		Terazosin	2	197.25	0.00	394.50
		Valsartan	16	451.37	112.53	7 221.87
	HCTZ/KCl	Methyldopa	6	85.91	21.77	515.44
		Prazosin	1	101.69	0.00	101.69
	HCTZ	Indapamide	4	104.10	36.95	416.39
		Methyldopa	9	177.39	66.48	1 596.50
		Nifedipine	16	317.30	63.38	5 076.86
		Perindopril	2	233.38	121.10	466.76
		Reserpine	1	128.98	0.00	128.98
	HCTZ/Triamterene	Israpidine	1	457.12	0.00	457.12
		Nifedipine	2	264.26	23.58	528.51
	Hydrolumethiazide/Reserpine	Indapamide	1	195.57	0.00	195.57
	Indapamide	Israpidine	24	317.47	128.72	7 619.33
		Methyldopa	13	201.59	87.51	2 620.67

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Indapamide	Nifedipine	17	367.44	76.10	6 246.51
		Piretanide	2	279.93	11.05	559.86
		Prazosin	1	112.69	0.00	112.69
		Reserpine	1	360.43	0.00	360.43
		Sotalol	1	212.49	0.00	212.49
		Spironolactone	6	100.57	41.03	603.41
		Torazemide	3	228.99	105.71	686.97
	Isosorbide	Spironolactone	3	368.03	52.00	1 104.08
	Methyldopa	Nifedipine	1	315.71	0.00	315.71
	Nifedipine	Prazosin	6	493.40	126.26	2 960.38
		Reserpine	4	316.23	81.79	1 264.90
		Sotalol	2	634.34	0.00	1 268.68
		Timolol/Amiloride	5	937.48	266.38	4 687.41
	Spironolactone	Torazemide	6	1212.23	618.72	7 273.40
Captopril/HCTZ	Carvedilol	Spironolactone	3	483.43	116.82	1 450.28
	Furosemide	Spironolactone	2	149.86	14.81	299.71
Cilazapril	Doxazosin	Furosemide	8	424.74	82.82	3 397.94
	Ezetimibe	Spironolactone	1	509.78	0.00	509.78
	Furosemide	Methyldopa	4	323.38	5.78	1 293.52
		Spironolactone	5	236.05	84.33	1 180.23
	Indapamide	Prazosin	2	266.98	0.05	533.95
		Trandolapril/Verapamil	1	600.61	0.00	600.61
	Spironolactone	Torazemide	6	524.57	173.67	3 147.42
Cilazapril/HCTZ	Furosemide	Moxonidine	1	987.78	0.00	987.78
	Methyldopa	Moxonidine	1	485.24	0.00	485.24
	Moxonidine	Nifedipine	1	840.19	0.00	840.19

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	**Enalapril**	HCTZ	12	133.92	25.00	1 607.05
		Indapamide	2	234.64	52.93	469.27
		Israpidine	1	400.51	0.00	400.51
		Methyldopa	1	204.81	0.00	204.81
		Prazosin	8	180.65	64.41	1 445.21
	Enalapril/HCTZ	Furosemide	8	191.84	45.81	1 534.75
		Reserpine	1	271.52	0.00	271.52
		Sotalol	8	229.86	32.21	1 838.91
		Spironolactone	1	317.14	0.00	317.14
	Ezetimibe	Furosemide	4	525.28	80.16	2 101.11
		Hydrochlorthiazide	3	318.46	230.41	955.37
		Indapamide	21	301.94	92.13	6 340.71
		Nebivolol	3	477.84	0.00	1 433.52
	Furosemide	Furosemide	1	748.92	0.00	748.92
		HCTZ/KCl	1	95.71	0.00	95.71
		HCTZ	1	359.09	0.00	359.09
		Indapamide	2	208.93	168.26	417.85
		Irbesartan	2	401.99	3.85	803.98
		Methyldopa	6	337.91	73.20	2 027.48
		Minoxidil	1	261.24	0.00	261.24
		Moxonidine	7	292.84	142.81	2 049.86
		Nifedipine	30	416.08	153.82	12 482.42
		Perindopril	1	186.97	0.00	186.97
		Quinapril/HCTZ	2	436.18	0.00	872.36
		Reserpine	4	103.40	1.50	413.59
		Sotalol	3	634.02	0.00	1 902.06
		Spironolactone	111	460.93	505.19	51 163.48
		Spironolactone/IsobutylHydrochlorthiazide	6	382.72	45.86	2 296.30
		Tamsulosin	1	758.76	0.00	758.76
		Terazosin	1	548.33	0.00	548.33

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	Hydralazine	HCTZ	1	82.93	0.00	82.93
		Prazosin	3	495.64	73.96	1 486.91
	HCTZ/KCl	Methyldopa	1	274.45	0.00	274.45
		Nifedipine	1	293.80	0.00	293.80
		Reserpine	13	111.09	36.53	1 444.20
	HCTZ/Valsartan	Nifedipine	1	547.67	0.00	547.67
	HCTZ	Nifedipine	10	433.01	161.84	4 330.11
		Prazosin	1	225.92	0.00	255.92
		Reserpine	23	75.35	24.26	1 732.98
	Hydrochlorthiazide/Triamterene	Labetalol	1	746.26	0.00	746.26
		Nifedipine	13	636.53	99.74	8 274.93
		Sotalol	6	259.79	24.95	1 558.72
	Hydroflumethiazide/Reserpine	Indapamide	1	191.49	0.00	191.49
	Indapamide	Israpidine	12	449.98	106.49	5 399.78
		Methyldopa	11	194.04	50.80	2 134.43
		Nifedipine	91	386.23	98.71	35 147.19
		Prazosin	13	184.45	58.62	2 397.85
		Reserpine	2	150.27	0.00	300.54
		Sotalol	23	209.19	74.04	4 811.27
		Tamsulosin	4	574.73	0.00	2 298.92
	Indapamide/Perindopril	Nifedipine	1	357.75	0.00	357.75
		Prazosin	1	548.08	0.00	548.08
	Isosorbide	Isosorbide	7	677.04	30.23	4 739.30
	Israpidine	Spironolactone	6	509.77	89.00	3 058.61
	Methyldopa	Nifedipine	4	356.47	84.54	1 425.88
	Nifedipine	**Quinapril/HCTZ**	10	449.81	62.30	4 498.13
		Spironolactone	5	382.82	69.46	1 914.12
		Torazemide	9	441.75	137.48	3 975.74
	Prazosin	Reserpine	2	309.00	0.00	618.00
	Spironolactone	Torazemide	1	239.71	0.00	239.71

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril/HCTZ	Ezetimibe	Furosemide	11	336.04	83.79	3 696.48
		Moxonidine	4	724.44	11.73	2 897.74
		Spironolactone	2	409.27	135.03	818.54
	Furosemide	HCTZ/KCl	5	127.82	47.31	639.10
		Indapamide/Perindopril	1	250.15	0.00	250.15
		Nifedipine	4	395.79	60.98	1 583.17
		Sotalol	1	277.18	0.00	277.18
		Spironolactone	11	179.77	35.90	1 977.49
	Hydralazine	Methyldopa	1	283.93	0.00	283.93
	HCTZ/KCl	Reserpine	1	103.58	0.00	103.58
	Indapamide	**Lisinopril**	1	279.07	0.00	279.07
		Methyldopa	7	197.99	35.61	1 385.90
		Minoxidil	6	255.00	69.82	1 530.00
		Nifedipine	13	522.35	115.86	6 790.60
		Prazosin	1	234.33	0.00	234.33
	Methyldopa	Nifedipine	16	424.66	124.50	6 794.54
	Metoprolol	Spironolactone	4	546.36	0.00	2 185.44
	Moxonidine	Prazosin	6	543.25	49.06	3 259.49
		Torazemide	4	388.87	77.09	1 555.48
	Nifedipine	Prazosin	6	329.30	10.28	1 975.81
		Reserpine	2	458.74	221.68	917.48
Felodipine/Ramipril	Furosemide	Spironolactone	16	520.76	184.01	8 332.16
	HCTZ/KCl	Nebivolol	1	434.11	0.00	434.11
	HCTZ	Reserpine	10	352.27	137.69	3 522.74
	Indapamide	Indapamide	1	425.80	0.00	425.80
		Moxonidine	1	737.63	0.00	737.63
		Nebivolol	6	610.69	74.15	3 664.11
	Indapamide	Sotalol	11	436.74	114.69	4 804.12
	Methyldopa	Moxonidine	1	877.83	0.00	877.83
	Moxonidine	Valsartan	6	944.82	52.90	5 668.91

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Fosinopril	Furosemide	Methyldopa	1	256.22	0.00	256.22
		Sotalol	3	687.88	95.71	2 063.65
		Spironolactone	3	727.30	0.00	2 181.90
	HCTZ	Sotalol	9	632.75	122.41	4 594.74
	Indapamide	Nifedipine	3	408.18	6.74	1 224.54
		Torazemide	2	391.78	0.55	783.56
	Irbesartan	Torazemide	1	645.94	0.00	645.94
Fosinopril/HCTZ	Irbesartan	Nifedipine	4	1174.95	24.00	4 699.81
Indapamide/Perindopril	Isosorbide	Nebivolol	4	793.38	11.85	3 173.51
	Israpidine	**Perindopril**	8	595.40	158.72	4 763.22
	Lisinopril	Methyldopa	8	450.41	32.70	3 603.28
	Methyldopa	Nifedipine	7	1014.04	235.38	7 098.27
	Metoprolol	Nifedipine	1	814.71	0.00	814.71
	Moxonidine	Nifedipine	1	652.07	0.00	652.07
		Perindopril	10	498.41	140.84	4 984.12
		Spironolactone	12	404.06	131.58	4 848.71
	Nifedipine	Nifedipine	1	904.94	0.00	904.94
		Perindopril	1	479.22	0.00	479.22
		Prazosin	15	15.00	560.52	8 407.80
		Quinapril/HCTZ	2	572.17	17.22	1 144.33
		Spironolactone	2	893.97	281.99	1 787.94
		Tamsulosin	1	664.69	0.00	664.69
		Telmisartan	14	804.35	83.39	11 260.90
	Prazosin	Sotalol	2	946.08	0.00	1 892.16
	Sotalol	Spironolactone	1	781.72	0.00	781.72
	Spironolactone	Torazemide	1	554.47	0.00	554.47
	Telmisartan	Telmisartan/HCTZ	1	703.32	0.00	703.32

Table C6 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Lisinopril	**Lisinopril**	Sotalol	7	361.36	42.72	2 529.55
	Nifedipine	Sotalol	4	415.64	30.50	1 662.57
		Spironolactone	1	388.31	0.00	388.31
		Telmisartan	3	635.68	56.72	1 907.04
	Prazosin	Reserpine	6	146.12	38.47	876.70
	Spironolactone	Timolol/Amiloride	4	401.88	25.07	1 607.52
Lisinopril/HCTZ	**Lisinopril/HCTZ**	Sotalol	4	460.94	2.73	1 843.74
	Metoprolol	Nebivolol	6	652.67	245.51	3 916.03
	Nebivolol	Nifedipine	11	549.12	82.73	6 040.30
	Nifedipine	Piretanide	9	593.05	100.24	5 337.48
		Tamsulosin	2	880.08	0.00	1 760.16
	Reserpine	Spironolactone	1	247.07	0.00	247.07
Moexipril	Spironolactone	Spironolactone	1	196.41	0.00	196.41
		Tamsulosin	3	523.10	43.58	1 569.31
Perindopril	Prazosin	Prazosin	1	642.52	0.00	642.52
	Reserpine	**Trandolapril/Verapamil**	1	479.42	0.00	479.42
	Spironolactone	Telmisartan	2	427.46	13.92	854.92
		Torazemide	46	402.74	168.41	18 526.10
		Valsartan	3	398.87	17.45	1 196.62
Quinapril	Spironolactone	Torazemide	2	501.66	96.80	1 003.31
Ramipril	Spironolactone	Torazemide	5	473.48	171.07	2 367.40
	Terazosin	Torazemide	9	744.03	262.07	6 696.29

Table C7: ACE inhibitor prescribed together with two other antihypertensive items for 2005.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	**Captopril**	HCTZ/Triamterene	10	80.33	0.00	803.30
	Carvedilol	Furosemide	15	185.34	81.89	2 780.15
		HCTZ/KCl	2	80.42	0.00	160.84
		Indapamide	1	202.21	0.00	202.21
		Spironolactone	15	161.50	32.58	2 422.44
	Doxazosin	Furosemide	1	322.68	0.00	322.68
		Nifedipine	2	502.22	0.00	1 004.44
	Ezetimibe	HCTZ/Triamterene	9	250.02	17.05	2 250.16
	Furosemide	Indapamide	2	92.40	106.72	184.80
		Isosorbide	3	305.46	29.64	916.37
		Methyldopa	4	118.13	0.00	472.52
		Nifedipine	2	468.53	0.00	937.06
		Prazosin	3	155.13	0.00	465.39
		Spironolactone	71	171.09	85.83	12 147.47
		Torazemide	1	608.27	0.00	608.27
	Hydrochlorthiazide	Methyldopa	12	93.41	0.71	1 120.92
		Nifedipine	1	321.43	0.00	321.43
		Reserpine	2	76.30	0.00	152.60
	Indapamide	Methyldopa	12	107.69	10.48	1 292.31
		Nifedipine	21	271.43	28.71	5 700.11
		Perindopril	1	171.34	0.00	171.34
	Methyldopa	Nifedipine	1	428.74	0.00	428.74
	Nifedipine	Prazosin	1	268.69	0.00	268.69
		Torazemide	1	567.10	0.00	567.10
Captopril/HCTZ	Carvedilol	Furosemide	1	171.48	0.00	171.48
	Felodipine/Ramipril	Indapamide	1	224.90	0.00	224.90
Cilazapril	Doxazosin	Furosemide	12	360.98	0.00	4 331.76
Cilazapril/HCTZ	Doxazosin	Isosorbide	4	465.38	0.00	1 861.52

Table C7 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2005.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	**Enalapril**	Indapamide	3	156.69	0.00	470.07
		Prazosin	8	174.66	14.94	1 397.26
		Sotalol	1	326.93	0.00	326.93
	Enalapril/HCTZ	HCTZ	1	110.47	0.00	110.47
		Nifedipine	2	411.18	0.00	822.36
		Spironolactone	6	168.51	0.00	1 011.06
	Ezetimibe	Furosemide	1	279.62	0.00	279.62
		Indapamide	8	241.22	0.00	1 929.76
		Spironolactone	4	290.04	0.00	1 160.16
	Furosemide	Furosemide	1	169.21	0.00	169.21
		HCTZ/KCl	3	95.71	0.00	287.13
		HCTZ	6	150.23	30.51	901.36
		Nifedipine	23	453.20	127.53	10 423.57
		Reserpine	1	94.74	0.00	94.74
		Spironolactone	49	204.25	106.19	10 008.39
	Hydralazine	Prazosin	1	317.02	0.00	317.02
	HCTZ/KCl	Prazosin	2	126.90	0.00	253.80
		Reserpine	12	94.03	29.07	1 128.39
	HCTZ/Valsartan	Indapamide	1	334.36	0.00	334.36
		Israpidine	4	597.59	0.00	2 390.36
		Nifedipine	3	443.65	13.72	1 330.95
	HCTZ	Nifedipine	26	258.54	84.76	6 722.14
		Perindopril	1	212.00	0.00	212.00
		Reserpine	1	55.74	0.00	55.74
		Spironolactone	1	110.54	0.00	110.54
		Tamsulosin	5	325.54	3.04	1 627.71
	Hydrochlorthiazide/Triamterene	Nifedipine	8	522.05	0.00	4 176.40
		Tamsulosin	6	374.71	0.00	2 248.26

Table C7 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2005.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	Indapamide	Israpidine	2	392.31	0.00	784.62
		Methyldopa	12	167.09	0.00	2 005.08
		Nifedipine	50	334.36	78.36	16 717.90
		Sotalol	9	156.67	11.54	1 410.03
	Indapamide/Perindopril	Nifedipine	1	514.77	0.00	514.77
	Isosorbide	Methyldopa	4	296.26	0.00	1 185.04
	Methyldopa	Nifedipine	1	597.60	0.00	597.60
	Nifedipine	**Quinapril/HCTZ**	8	350.18	0.00	2 801.44
	Spironolactone	Telmisartan	5	552.68	184.15	2 763.38
		Torazemide	28	256.90	13.44	7 193.18
Enalapril/HCTZ	Furosemide	HCTZ/KCl	1	105.96	0.00	105.96
		Nifedipine	5	405.52	27.98	2 027.62
		Spironolactone	15	131.63	3.30	1 974.49
	HCTZ/KCl	Reserpine	1	51.40	0.00	51.40
	Indapamide	Nifedipine	4	361.17	0.00	1 444.68
	Metoprolol	Spironolactone	5	178.32	3.53	891.62
	Moxonidine	Torazemide	10	379.99	11.44	3 799.90
	Nifedipine	Prazosin	8	322.64	17.31	2 581.12
	Spironolactone	Torazemide	9	301.56	3.92	2 714.04
Felodipine/Ramipril	Furosemide	Spironolactone	1	252.59	0.00	252.59
	Indapamide	Moxonidine	9	459.82	2.25	4 138.42
		Prazosin	1	292.94	0.00	292.94
		Sotalol	11	383.53	0.00	4 218.83
	Indapamide/Perindopril	Nifedipine	5	901.77	0.52	4 508.86
	Irbesartan	Nifedipine	1	827.49	0.00	827.49

Table C7 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2005.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Fosinopril	HCTZ	Nifedipine	1	421.19	0.00	421.19
Indapamide/Perindopril	Irbesartan	Nifedipine	9	627.20	15.41	5 644.84
		Spironolactone	1	503.71	0.00	503.71
	Israpidine	Nifedipine	2	779.57	0.00	1 559.14
		Perindopril	6	535.87	0.00	3 215.22
	Methyldopa	Nifedipine	2	795.53	0.00	1 591.06
	Minoxidil	Nifedipine	2	723.67	0.00	1 447.34
	Moxonidine	Nifedipine	1	652.12	0.00	652.12
		Perindopril	10	508.06	0.00	5 080.60
		Spironolactone	2	789.02	0.00	1 578.04
	Nifedipine	**Perindopril**	6	498.61	0.00	2 991.67
		Prazosin	9	573.39	115.27	5 160.49
		Spironolactone	1	572.61	0.00	572.61
		Telmisartan	23	820.75	27.76	18 877.36
		Timolol/Amiloride	1	637.62	0.00	637.62
	Spironolactone	Torazemide	12	465.19	35.22	5 582.26
Lisinopril	Nifedipine	Spironolactone	3	378.30	42.84	1 134.90
Lisinopril/HCTZ	**Lisinopril/HCTZ**	Sotalol	10	380.43	91.83	3 804.30
	Minoxidil	Nifedipine	2	634.14	0.00	1 268.28
	Nebivolol	Nifedipine	12	470.13	25.91	5 641.61
	Nifedipine	Piretanide	7	347.72	99.87	2 434.02
Perindopril	Piretanide	Spironolactone	2	187.88	70.44	375.76
		Tamsulosin	8	550.24	0.00	4 401.92
	Reserpine	Spironolactone	3	247.88	0.00	743.64
		Telmisartan	3	439.84	0.00	1 319.52
	Spironolactone	Torazemide	11	363.59	71.39	3 999.52
Ramipril	Spironolactone	Torazemide	20	427.31	31.88	8 546.23

Table C8: ACE inhibitor prescribed together with two other antihypertensive items for 2006.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Carvedilol	Furosemide	1	212.10	0.00	212.10
	Doxazosin	Furosemide	5	322.68	0.00	1 613.40
	Furosemide	Indapamide	5	142.83	4.91	714.13
		Spironolactone	10	107.34	68.24	1 073.37
	HCTZ/Triamterene	Tamsulosin	8	475.84	52.65	3 806.75
	Indapamide	**Perindopril**	1	187.42	0.00	187.42
	Indapamide/Perindopril	Nifedipine	1	454.12	0.00	454.12
	Nifedipine	**Quinapril/HCTZ**	1	358.30	0.00	358.30
Captopril/HCTZ	Carvedilol	Spironolactone	2	191.55	0.00	383.10
	Indapamide	**Indapamide/Perindopril**	1	509.23	0.00	509.23
Enalapril	**Enalapril**	Indapamide	1	157.83	0.00	157.83
		Nifedipine	1	374.87	0.00	374.87
		Spironolactone	4	110.15	0.00	440.60
	Ezetimibe	Indapamide	3	354.99	0.00	1 064.97
	Furosemide	Metoprolol	1	294.14	0.00	294.14
		Nifedipine	5	513.34	10.08	2 566.68
		Spironolactone	7	131.54	38.97	920.81
	HCTZ/Valsartan	Israpidine	11	597.59	0.00	6 573.49
	HCTZ	Tamsulosin	2	326.90	0.00	653.80
	Indapamide	Losartan/HCTZ	2	357.87	12.32	715.73
		Nifedipine	23	399.06	48.06	9 178.33
		Tamsulosin	4	364.42	19.37	1 457.67
	Indapamide/Perindopril	Nifedipine	2	450.66	39.24	901.32
Enalapril/HCTZ	Furosemide	Nifedipine	1	352.09	0.00	352.09
		Spironolactone	6	233.21	41.14	1 399.26
	Indapamide	Nifedipine	1	369.84	0.00	369.84
	Metoprolol	Spironolactone	4	474.32	0.00	1 897.28
	Moxonidine	Torazemide	6	369.71	8.11	2 218.25

Table C8 (continued): ACE inhibitor prescribed together with two other antihypertensive items for 2006.

Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Felodipine/Ramipril	Furosemide	Spironolactone	1	252.59	0.00	252.59
	Indapamide	Spironolactone	2	342.44	54.87	684.88
	Indapamide/Perindopril	Nifedipine	3	901.54	0.00	2 704.62
Indapamide/Perindopril	Irbesartan	Nifedipine	5	707.13	0.02	3 535.64
	Israpidine	Nifedipine	3	647.10	0.00	1 941.30
	Methyldopa	Nifedipine	5	626.38	115.97	3 131.89
	Metoprolol	Nifedipine	1	875.33	0.00	875.33
	Minoxidil	Nifedipine	11	682.74	13.57	7 510.17
	Moxonidine	Spironolactone	1	789.02	0.00	789.02
	Nifedipine	Prazosin	14	617.85	87.66	8 649.84
		Spironolactone	8	612.99	14.90	4 903.94
		Telmisartan	21	797.59	36.63	16 749.32
		Terazosin	1	634.93	0.00	634.93
		Valsartan	4	441.50	0.00	1 766.00
	Ramipril	**Ramipril**	3	420.04	0.00	1 260.12
	Spironolactone	Tamsulosin	1	612.68	0.00	612.68
Lisinopril	**Lisinopril**	Spironolactone	1	87.07	0.00	87.07
	Metoprolol	Nifedipine	8	602.87	0.00	4 822.96
Perindopril	Reserpine	Spironolactone	2	247.88	0.00	495.76
		Telmisartan	4	439.84	0.00	1 759.36
	Spironolactone	Tamsulosin	10	522.70	26.59	5 227.02
		Torazemide	4	311.46	148.92	1 245.83
Ramipril	**Ramipril**	Spironolactone	1	236.80	0.00	236.80

Table C9: ACE inhibitor prescribed together with three other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazpril	Carvedilol	Ezetimibe	Indapamide	2	812.35	22.81	1 624.70
Captopril	**Captopril**	Furosemide	Spironolactone	1	303.54	0.00	303.54
	Captopril/HCTZ	Dihydroergocristine/Clopamide	Indapamide	12	633.32	8.22	7 599.81
	Carvedilol	Furosemide	HCTZ	1	565.45	0.00	565.45
			Spironolactone	29	521.30	251.50	15 117.76
	Dihydroergocristine/Clopamide	Indapamide	Nifedipine	14	814.99	32.28	11 409.89
	Doxazosin	Furosemide	Metolazone	1	872.68	0.00	872.68
			Spironolactone	6	550.41	113.19	3 302.45
	Furosemide	HCTZ/Triamterene	Nifedipine	6	664.49	3.61	3 986.91
		Indapamide	Methyldopa	9	479.92	17.53	4 319.27
			Nifedipine	2	518.70	0.00	1 037.40
		Indoramin	Spironolactone	11	820.13	53.02	9 021.41
		Israpidine	Spironolactone	8	569.48	28.45	4 555.81
		Methyldopa	Nifedipine	6	916.15	291.00	5 496.90
			Prazosin	1	972.39	0.00	972.39
			Reserpine	4	752.86	9.12	3 011.43
		Metolazone	Spironolactone	2	897.01	203.54	1 794.01
		Nifedipine	Spironolactone	3	1070.80	43.56	3 212.39
		Sotalol	Spironolactone	2	437.75	0.00	875.50
	Hydralazine	HCTZ	Methyldopa	1	188.40	0.00	188.40
		Nifedipine	Reserpine	1	568.80	0.00	568.80
	HCTZ	Israpidine	Nifedipine	1	659.98	0.00	659.98
	HCTZ/Triamterene	Labetalol	Minoxidil	3	1413.50	1.75	4 240.51
Captopril/HCTZ	Carvedilol	Furosemide	Spironolactone	2	681.22	0.00	1 362.44
	Methyldopa	Nifedipine	Nifedipine	3	939.04	68.92	2 817.11

Table C9 (continued): ACE inhibitor prescribed together with three other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	**Enalapril/HCTZ**	Nifedipine	Piretanide	18	723.26	111.24	13 018.72
	Ezetimibe	HCTZ	Methyldopa	1	691.50	0.00	691.50
	Furosemide	Hydralazine	Methyldopa	1	327.72	0.00	327.72
		Indapamide	Prazosin	2	288.17	0.00	576.34
		Isosorbide	Metolazone	1	1019.79	0.00	1 019.79
		Methyldopa	Metolazone	1	2828.80	0.00	2 828.80
			Nifedipine	3	590.20	0.61	1 770.61
		Nifedipine	Prazosin	6	1313.62	169.64	7 881.71
		Perindopril	Spironolactone	1	514.07	0.00	514.07
	Indapamide	Nifedipine	Nifedipine	33	803.08	131.43	26 501.62
		Spironolactone	**Trandolapril/Verapamil**	1	690.18	0.00	690.18
Enalapril/HCTZ	Nifedipine	Prazosin	Prazosin	1	949.61	0.00	949.61
Fosinopril	Furosemide	Metolazone	Spironolactone	1	477.20	0.00	477.20
Indapamide/Perindopril	**Lisinopril**	Methyldopa	Nifedipine	6	961.01	27.13	5 766.07
Lisinopril	Nifedipine	Sotalol	Spironolactone	10	527.12	25.21	5 271.45
Perindopril	Piretanide	Piretanide	Spironolactone	4	477.41	0.00	1 909.64

Table C10: ACE inhibitor prescribed together with three other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazepril	Carvedilol	Ezetimibe	Indapamide	10	707.44	126.38	7 074.39
Benazepril/HCTZ	Furosemide	Spironolactone	Telmisartan	2	676.34	0.00	1 352.68
Captopril	Carvedilol	Doxazosin	Furosemide	9	167.60	40.31	1 508.43
		Furosemide	Furosemide	1	586.99	0.00	586.99
			HCTZ	6	243.21	20.25	1 459.24
			Spironolactone	22	389.86	192.31	8 576.85
	Ezetimibe	Furosemide	Spironolactone	1	419.43	0.00	419.43
		HCTZ	Terazosin	8	1047.56	244.89	8 380.46
	Furosemide	Furosemide	Spironolactone	3	313.83	36.12	941.49
		HCTZ	Methyldopa	1	172.42	0.00	172.42
		Indapamide	Methyldopa	7	350.52	68.39	2 453.63
		Methyldopa	Reserpine	12	178.09	88.46	2 137.10
		Prazosin	Spironolactone	1	264.98	0.00	264.98
	Hydralazine	Indapamide	Nifedipine	1	418.43	0.00	418.43
	HCTZ	Methyldopa	Nifedipine	2	462.28	0.00	924.56
		Reserpine	Spironolactone	2	234.60	5.85	469.20
Cilazapril	Doxazosin	Furosemide	Spironolactone	3	640.22	0.00	1 920.66
	Ezetimibe	Prazosin	Timolol/Amiloride	1	803.13	0.00	803.13
Cilazapril/HCTZ	Furosemide	Moxonidine	Nifedipine	1	939.62	0.00	939.62
	Methyldopa	Moxonidine	Nifedipine	2	811.96	49.72	1 623.92

Table C10 (continued): ACE inhibitor prescribed together with three other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Enalapril	**Enalapril/HCTZ**	Furosemide	Nifedipine	4	408.74	2.93	1 634.97
		Moxonidine	Prazosin	2	558.43	0.00	1 116.86
		Nifedipine	Piretanide	7	412.27	48.50	2 885.91
		Spironolactone	Torazemide	4	487.71	4.24	1 950.84
	Ezetimibe	Spironolactone	Torazemide	2	297.48	25.29	1 194.96
	Furosemide	Hydrochlorthiazide	Reserpine	1	74.74	0.00	74.74
		HCTZ/Triamterene	Sotalol	2	399.84	174.76	799.67
		Indapamide	Methyldopa	1	281.08	0.00	281.08
		Irbesartan	Nifedipine	1	444.95	0.00	444.95
		Methyldopa	Reserpine	1	213.76	0.00	213.76
		Nifedipine	Prazosin	4	865.94	51.52	3 463.76
		Piretanide	Spironolactone	1	285.40	0.00	285.40
		Prazosin	Spironolactone	2	300.16	0.00	600.32
	HCTZ/Valsartan	HCTZ/Triamterene	Labetalol	2	904.68	77.76	1 809.35
	HCTZ	Nifedipine	Reserpine	3	231.14	0.36	693.42
	Indapamide	Irbesartan	Nifedipine	1	562.80	0.00	562.80
		Nifedipine	Nifedipine	7	590.48	82.80	4 133.38
	Nifedepine	Spironolactone	Torazemide	4	468.69	38.27	1 874.77
Enalapril/HCTZ	Furosemide	**Indapamide/Perindopril**	Spironolactone	3	670.32	314.12	2 010.97
Indapamide/Perindopril	Israpidine	**Perindopril**	Valsartan	1	849.40	0.00	849.40
	Methyldopa	Moxonidine	Nifedipine	2	1055.51	206.08	2 111.02
	Nifedepine	Prazosin	Spironolactone	3	938.14	59.58	2 814.42
Lisinopril	Minoxidil	Prazosin	Torazemide	1	1337.57	0.00	1 337.57

Table C11: ACE inhibitor prescribed together with three other antihypertensive items for 2005.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Carvedilol	Furosemide	Indapamide	1	168.02	0.00	168.02
			Spironolactone	1	221.35	0.00	221.35
		Nifedipine	Spironolactone	1	613.80	0.00	613.80
		Spironolactone	Torazemide	2	276.60	0.00	553.20
	Furosemide	Methyldopa	Reserpine	9	127.94	5.32	1 151.42
	Indapamide	Methyldopa	Nifedipine	15	353.62	139.17	5 304.34
Captopril/HCTZ	Carvedilol	Furosemide	Spironolactone	1	240.29	0.00	240.29
Enalapril	**Enalapril/HCTZ**	Furosemide	Nifedipine	12	413.19	0.00	4 958.28
	Ezetimibe	Furosemide	Sotalol	1	609.30	0.00	609.30
		Spironolactone	Tamsulosin	1	505.87	0.00	505.87
	Furosemide	Indapamide	Prazosin	5	157.09	0.00	785.45
			Valsartan	1	347.74	0.00	347.74
		Methyldopa	Nifedipine	1	577.49	0.00	577.49
		Metoprolol	Spironolactone	3	278.81	42.75	836.42
		Nifedipine	**Perindopril**	1	503.09	0.00	503.08
	Reserpine	Spironolactone	Telmisartan	1	897.08	0.00	897.08

Table C12: ACE inhibitor prescribed together with three other antihypertensive items for 2006.

Active ingredient	Active ingredient	Active ingredient	Active ingredient	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Doxazosin	Furosemide	Spironolactone	6	394.18	0.00	2 365.08
Enalapril	Furosemide	Metoprolol	Spironolactone	1	303.49	0.00	303.49
		Nifedipine	Reserpine	2	461.92	0.00	923.84

Table C13: ACE inhibitor prescribed together with four other antihypertensive items for 2001-2002.

Active ingredient	Active ingredient	Active ingredients	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Doxazosin	Furosemide+Nisoldipine+ Spirinolactone	4	1182.89	2.65	4 731.54
	Furosemide	Hydralazine+Nifedipine+ Reserpine	13	574.01	29.27	7 462.09
Enalapril	Furosemide	Indapamide+Nifedipine+ Nifedipine	1	874.83	0.00	874.83

Table C14: ACE inhibitor prescribed together with four other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredients	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Benazepril	Bumetanide/KCL	Doxazosin+Moxonidine+ Nifedipine	11	1072.81	167.24	11 800.94
Captopril	Carvedilol	Furosemide+Spironolactone+ Torazemide	4	980.16	4.24	3 920.64
		Furosemide+Spironolactone+ Valsartan	1	745.29	0.00	745.29
Cilazapril/HCTZ	Furosemide	Methyldopa+Moxonidine+ Nifedipine	3	1002.01	0.02	3 006.02
Enalapril	**Enalapril/HCTZ**	Furosemide+Nifedipine+ Tamsulosin	2	761.43	153.34	1 522.86
	Ezetimibe	Furosemide+Furosemide+ Spironolactone	4	645.83	43.88	2 583.32
	Indapamide	Irbesartan+Nebivolol+ Reserpine	4	466.18	22.24	1 864.73

Table C15: ACE inhibitor prescribed together with five other antihypertensive items for 2004.

Active ingredient	Active ingredient	Active ingredients	Frequency (N)	Average cost/ combination(R)	Standard devation (±)	Total cost (R)
Captopril	Furosemide	Hydrochlorothiazide+Prazosin+ Reserpine+Spironolactone	5	355.28	33.48	1 776.42

Appendix D

Prescribing patterns of angiotensin-converting enzyme inhibitors for the period 2001 until 2006

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Purpose:

The general objective of this study was to investigate the prescribing patterns and cost of angiotensin-converting enzyme (ACE) inhibitors in the private sector for the period 2001 until 2006, by using a medicine claims database.

Method:

A longitudinal retrospective drug utilisation study was done on ACE inhibitors claimed through a national medicine claims database for 2001-2002, 2004, 2005 and 2006. The periods 2004, 2005 and 2006 were further divided into January to April, May to August and September to December. The data were analysed by using the Statistical Analysis System®, SAS 9.1 (SAS for Windows, 9.1, 2006).

Results:

The ACE inhibitors represented 4.07% (n=R39 938 139.33) of the total cost of all medicine items (N =R 981 058 815.00) claimed for *2001 to 2002*. For *2004* ACE inhibitors represented 4.40% (n=R29 100 326.90) of all items (N =R661 221 000.00) claimed, and then decreased to 3.92% (n=R15 893 890.26) for *2005* (N =R405 829 097.00) and further decreased to 3.42% (n=R9 552 425.76) of the total cost (N=R 279 160 832.00) for 2006.

The highest average cost per ACE inhibitor item was R186.74±R97.20 and was for *January to April 2004*, and the lowest average cost of R134.60±R73.83 during *September to December 2004*. *January to April 2006* showed the highest increase in average cost of 14.49% from the previous period. The d-values between *2004* and *2005* as well as between *2005* and *2006* were of no practical significance where d<0.8.

The ACE inhibitor innovators represented 76.10% (n=151 370) of all the ACE inhibitor items (N=198 922) claimed for *2001 to 2002*. During the period of *2004*, ACE inhibitor innovators represented 61.02% (n=112 285) of all the items (N=184 018) claimed, and decreased to 55.87% (n= 58 993) of all the ACE inhibitor items (N=105 571) for *2005* and showed a slight increase to 57.79% (n= 32 315) of all the ACE inhibitor items (N=55 910) during *2006*.

Conclusion:

The contribution of ACE inhibitors with regard to the total cost showed a constant decrease from *2004* to *2006*. Prescribing of ACE inhibitor innovators showed a decrease from *2004* to *2005* and an increase to 2006, which shows an increase in generic prevalence from *2004* to *2005*. The difference between the average cost of all ACE inhibitor items between *2004* and *2005* as well as between *2005* and *2006* showed d-values<0.8 and therefore indicated that it is of no practical significance. *January to April 2005* showed an increase in the average cost, which was in the period of the Constitutional Court decision that the pricing regulations be set aside. *January to April 2006* showed an increase in the average cost possibly due to the pricing regulations being declared invalid. The implications of generic substitution with regard to prescribing patterns and cost need further investigation.