Usage patterns and cost analysis of angiotensin-converting enzyme (ACE) inhibitors using a medical aid claims database

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ABSTRACT

Key words: angiotensin-converting enzyme inhibitors
hypertension
cost benefit
cost-effectiveness

ACE inhibitors have been widely used in the treatment of certain diseases of the cardiovascular system, the major use being hypertension, since all ACE inhibitors are prescribed for its treatment. ACE inhibitors is also used in the treatment of congestive heart failure.

The angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II and also stimulates the production of aldosterone (a hormone produced in the adrenal glands that influences salt and water retention by the kidneys, increasing blood volume and blood pressure).

The cost benefit, cost-effectiveness and cost utility of ACE inhibitors have not been established. The objective of the study was to review and analyse the cost of ACE inhibitors by using a medical aid claims database.

Data for the study population consisted of all prescriptions containing one or more ACE inhibitor combinations and were extracted from the central database of Interpharm datasystems® for a period of one year, from 1 January 2001 to 31 December 2001. A total of 1 475 532 prescriptions containing a total of 2 953 244 ACE inhibitor items represented the study population.

Through the analysis of the general medicine utilisation patterns that were obtained from the medicine claims database, it became evident that ACE inhibitor utilisation contributes considerably to the total prevalence and cost of all the medicine items available on the database. It constituted a total prevalence of 4,62% (n =1 475 532) of

all the prescriptions and a total prevalence of 2,31% (n =2 953 244) for all the medicine items in the prescriptions with a cost of 3,65% (n =R379 911 472,00).

It was concluded that in the analysis of ACE inhibitors according to the innovator/generic classification, the majority of ACE inhibitors prescribed during the twelve-month period were for the innovator product, with a prevalence of 82,56% (n =68 162) and a cost of 89,11% (n =R13 863 080, 90). The utilisation of the generic ACE inhibitors, with a prevalence of 17,44% (n =68 162) and at a cost of 10,89% (n =R13 863 080, 90), was under-utilised. If the total number of prescriptions containing innovator ACE inhibitors could be generically substituted, (37,54%) R5 204 392,68 in cost expenditure could be saved over a twelve-month period. However, the fact that not all the innovator ACE inhibitors have generic equivalents available must be taken into account. 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. This was found by adding all the costs saved by substituting innovator drugs with their generics.

Consequently, it can be concluded that the extensive use of the innovator ACE inhibitors could mean an exceptional increase in the cost expenditure associated with ACE inhibitor therapy.

In completion of the study, recommendations were formulated as an aim to optimise the utilisation of ACE inhibitor generic equivalents.

OPSOMMING

Sleutelwoorde: angiotensien-omsettingsensiem (AOE)-inhibeerders
hipertensie
koste-voordeel
koste-effektiwiteit

AOE-inhibeerders word wyd gebruik vir die behandeling van sekere siektetoestande van die kardiovaskulêre stelsel, waarvan die hoofgebruik hipertensie is, omdat alle AOE-inhibeerders vir die behandeling hiervan voorgeskryf word. AOE-inhibeerders word verder ook gebruik vir die behandeling van kongestiewe hartversaking.

Die angiotensien-omsettingsensiem (AOE) skakel angiotensien I om in angiotensien II en stimuleer ook die produksie van aldosteroon ('n hormoon wat in die bynier geproduseer word en wat sout- en waterretensie deur die niere beïnvloed en bloedvolume en bloeddruk verhoog).

Die koste-voordeel, koste-effektiwiteit en koste aan die gebruik van AOE-inhibeerders is nog nie vasgestel nie. Die doel van hierdie studie was om die koste van AOE-inhibeerders te bestudeer en te ontleed deur gebruik te maak van 'n mediese-eisedatabasis.

Data vir die studiepopulasie het bestaan uit alle voorskrifte wat een of meer AOE-inhibeerder bevat het. Data is onttrek van die sentrale databasis van Interpharm datasystems® oor 'n periode van een jaar, van 1 Januarie 2001 tot 31 Desember 2001. 'n Totaal van 147 5532 voorskrifte wat 'n totaal van 295 3244 AOE-inhibeerder items bevat het, verteenwoordig die studiepopulasie.

Deur die ontleding van die algemene medisynegebruikspatrone wat uit die medisyne-eisedatabasis verkry is, het dit geblyk dat die gebruik van AOE-inhibeerders grootliks bydra tot die totale voorkoms en koste van al die medisyne-items beskikbaar in die databasis. Dit het 'n totale voorkoms van 4,62% (n = 1 475

532) verteenwoordig van al die voorskrifte en 'n totale voorkoms van 2,31% (n = 2 953 244) vir al die medisyne-items op die voorskrifte met 'n koste van 3,65% (n = R379 911 472,00).

Daar is tot die gevolgtrekking gekom dat in die ontleding van AOE-inhibeerders volgens 'n innoveerder- / generiese klassifikasie, die meerderheid van AOE-inhibeerders voorgeskryf gedurende die periode van twaalf maande- vir die innoveerder-produk was, met 'n voorkoms van 82,56% (n = 68 162) en 'n koste van 89,11% (n = R13 863 080,90). Die generiese AOE-inhibeerders is ondergebruik, met 'n voorkoms van 17,44% (n = 68 162) en 'n koste van 10,89% (n = R13 863 080,90). Die totale aantal voorskrifte wat innoveerder-AOE-inhibeerders bevat kon egter deur die generiese produk vervang word, en sou R5 204 392,68 (37,54%) oor periode van twaalf maande bespaar. Die feit dat nie al die innoveerder AOE-inhibeerders generiese ekwivalente het nie, moet in aanmerking geneem word. Indien slegs die voorskrifte wat generiese ekwivalente van AOE-inhibeerders bevat vervang word met hulle generiese ekwivalente, sou R899 751.29 (6.5%) bespaar word. Dit is bereken deur die som van al die kostes gespaar deur die oorspronklike innoveerder-AOE-inhibeerders met hulle generiese ekwivalente te vervang.

Gevolglik kan afgelei word dat die uitgebreide gebruik van die innoveerder-AOE-inhibeerders tot 'n aansienlike toename in die totale medisyne koste kan lei wat met AOE-inhibeerderterapie gepaard gaan.

In die voltooiing van hierdie studie word aanbevelings gedoen met die doel om die gebruik van AOE-inhibeerders se generiese ekwivalente te optimaliseer.

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

The focus of this study is on the analysis of the cost and usage patterns of angiotensin-converting enzyme (ACE) inhibitors.

1.2 BACKROUND

ACE inhibitors have been widely used in the treatment of certain diseases of the cardiovascular system, the major use being for hypertension, since all ACE inhibitors are prescribed for its treatment. The other use of ACE inhibitors is for the treatment of congestive heart failure (Snyman, 2002:134).

- **Problem statement**

The cost analysis (cost benefit, cost-effectiveness and cost utility) of ACE inhibitors have not been established. The aim of this research is to analyse the cost and the usage patterns of ACE inhibitors in the treatment of hypertension and congestive heart failure.

1.3 ACE INHIBITORS

ACE inhibitors are drugs that interfere with the action of the angiotensin-converting enzyme (ACE). This enzyme converts angiotensin I into angiotensin II and also stimulates the production of aldosterone (a hormone produced in the adrenal glands and which influences salt and water retention by the kidneys, increasing blood volume and blood pressure). An ACE inhibitor inhibits these actions thereby decreasing blood pressure and preventing congestive heart failure (Wood & Griffith, 1997:260).

1.3.1 Hypertension

Hypertension is another name for elevated blood pressure or high blood pressure (HBP). It is a serious condition that could lead to stroke, heart disease, kidney failure and other health problems. As blood flows from the heart to the blood vessels, it creates pressure against the blood vessel walls. A person's blood pressure reading is a measure of this pressure. When that reading rises above a certain level, it is called hypertension (Anon, 2002a:1).

Elevated diastolic blood pressure has commonly been used to define hypertension. This arbitrary choice was based on the fact that diastolic blood pressure was used as the criterion for the inclusion in most randomised therapeutic trials, including those on mild hypertension. However, systolic values are as important, as the cardiovascular risk is as strongly associated with systolic as with diastolic values, with no evidence of a threshold below which a decrease in systolic pressure does not reduce risk (WHO, 1996:4).

The average blood pressure reading for adults is 120/80 mm Hg, systolic / diastolic. A slightly higher or lower reading on both readings may not be a problem. If blood pressure goes above 140/90 mm Hg, however, some form of intervention might be needed. Lower blood pressure readings (for example, 110/70 mm Hg) are thought to be safe for most people. In adults the systolic BP reading is often high, while the diastolic BP reading is normal. This condition is called isolated systolic hypertension, and should also be treated. Studies prove that lowering the systolic measure cuts down on strokes and heart attacks in people aged 60 and over (Anon, 2002c:1).

In both young and older adults, the initial blood pressure levels largely determine the blood pressure increase as these persons' age increases. However, in aging, isolated systolic hypertension deserves special consideration. It may be viewed as a concomitant of aging, being quite infrequent until the mid-fifties, rising further with advancing age and carrying an increase with the risk of cardiovascular disease (WHO, 1983:10).

However, absolute blood pressure levels vary with gender, age, race and numerous other factors. The rate of progression of hypertension varies from one individual to another depending on the genetic and environmental background (WHO, 1978:8).

The percentage of individuals that are hypertensive with age is greater in blacks than in whites, but because blood pressure in many individuals is highly variable - especially in the office setting - the diagnosis of hypertension should be made only after elevation has been noted on three readings on different occasions, over a period of several months unless the elevations are severe or associated with symptoms (Massie, 2001:448).

High blood pressure is a major factor in the development of coronary heart disease and stroke, thus reducing it to normal levels is the prime concern in high risk cardiac patients (Massie, 2001:448). Continued hypertension does not necessarily indicate the need for pharmacological treatment. The decision to initiate drug therapy should be based on the assessment of overall cardiovascular risk rather than the level of blood pressure alone (Massie, 2001:448).

There are different classes of antihypertensive drugs of which five (ACE inhibitors, diuretics, beta-blockers, calcium channel blockers and angiotensin II receptor antagonists) are suitable for initial and single-drug therapy. The focus of this research is on ACE inhibitors. The ACE inhibitors are the agents of choice in patients with "end-stage" renal disease. The advantage of ACE inhibitors is their relative freedom from troublesome side effects (Massie, 2001:448).

1.3.2 Congestive heart failure

Circulatory failure has been classified into acute and chronic forms. The acute form is the circulatory failure that includes shock, syncope and sudden death, whereas the chronic form of circulatory failure is known as congestive heart failure (Friedberg, 1962:124). Congestive heart failure may be defined as the inability of the heart to pump adequate blood into the arterial system with resulting engorgement in the greater or lesser venous circuits. In general, chronic congestive heart failure is the result of severe primary depression of myocardial contractility or extreme ventricular haemodynamic overloading combined with a secondary diminution of contractile state (Mason, 1976:293).

It occurs when the cardiac output is inadequate to provide the oxygen needed by the body, although it is believed that the primary defect in early heart failure resides in the excitation-contraction coupling machinery of the heart. The clinical condition also involves many other processes and organs, including the baro-receptor reflex, the sympathetic nervous system, the

kidneys, the rennin-angiotensin-aldosterone system, vasopressin, and death of cardiac cells (Katzung, 1998:199).

Congestive heart failure is a syndrome with multiple causes that may involve the right ventricle, the left ventricle, or both. Cardiac output in congestive heart failure is usually below the normal range. This ventricular dysfunction may be primarily systolic (i.e. inadequate force generation to eject blood normally) or diastolic (i.e. inadequate relaxation to permit normal filling). Systolic dysfunction, with reduced cardiac output and significantly reduced ejection fraction (less than 45%), is typical of acute failure, especially that resulting from myocardial infarction (Katzung, 1998:199).

The use of ACE inhibitors for the treatment of congestive heart failure has shown beneficial actions in that these drugs both improve the cardiac pump function and reduce fluid retention and central venous pressure. Thus in these patients, ACE inhibitors produce significant reductions in peripheral vascular resistance via decreased angiotensin II, non-epinephrine levels and left ventricular filling pressure. These inhibitors also attenuate symptoms of congestive heart failure and reduce mortality and probably prevent the occurrence of heart failure, at least in patients with systolic dysfunction due to myocardial infarction (McAreavey & Robertson, 1990:327).

1.4 RESEARCH OBJECTIVES

This research consists of general and specific objectives.

- **General objective**

The general objective of this study is to review and analyse the usage patterns and cost of ACE inhibitor items by using a medical aid claims database.

- **Specific objectives**

The specific objectives are to

1. conceptualise the use of ACE inhibitors in the treatment of hypertension and congestive heart failure from available literature;
2. investigate the methods and techniques that are utilised in healthcare, in order to ensure cost-effective drug use from available literature;
3. review the total cost of ACE inhibitor items derived from the database;
4. determine the prevalence and usage patterns of ACE inhibitors as well as the costs associated with these drugs from the database;
5. identify and analyse the different innovator forms of ACE inhibitors with their different generic equivalents from the database;
6. determine the prevalence and costs associated with innovator and generic drugs of the ACE inhibitor agents from the database;
7. identify combination (mono or double) alternatives of ACE inhibitor items and to determine the costs associated with these combinations from the database; and
8. formulate recommendations regarding the utilisation patterns of ACE inhibitor drugs (both innovator and generics).

1.5 RESEARCH METHOD

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

1.5.1 Literature review

The literature review will focus on the following:

- The management of hypertension and congestive heart failure, focussing mostly on the ACE inhibitor items.

- Treatment of hypertension and congestive heart failure by using ACE inhibitor items and their possible generic therapy.

1.5.2 Empirical investigation

The empirical investigation consists of seven steps, namely:

- Selection of research design.
- Composition of the study population.
- The selection and application of criteria instruments for data analysis.
- Data analysis.
- Reliability and validity.
- The report and discussion of the results of the empirical investigation.
- Conclusion and recommendations based on the results of empirical investigation.

1.6 SUMMARY

Elevated blood pressure or high blood pressure (HBP) is a serious condition that could lead to stroke, heart disease, kidney failure and other health problems whereas congestive heart failure may be defined as the inability of the heart to pump adequate blood into the arterial system. ACE inhibitors are drugs that interfere with the action of the angiotensin-converting enzyme (ACE) thereby decreasing blood pressure and preventing congestive heart failure.

The findings from this literature study on cardiac diseases are based on research from as early as the 1960s, when data were sometimes never updated due to the same findings in research. This was to show that cardiac diseases do not change over time. The same problems and results are duplicates of the past findings. Therefore, in conclusion, it was found to be necessary to include all the literature from as far back as could be found.

CHAPTER 2

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AND CARDIAC DISEASES.

2.1. INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors now serve as established therapy in two of the most common cardiovascular conditions, namely hypertension and congestive heart failure. 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. 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).

2.2. ANGIOTENSIN CONVERTING ENZYME INHIBITORS

2.2.1. Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors in medication interfere with the action of angiotensin-converting enzyme (ACE); this enzyme converts angiotensin I into angiotensin II which stimulates the production of aldosterone (Wood & Griffith, 1997: 260).

2.2.2. General information

Angiotensin-converting enzyme inhibitors form part of a group of effective drugs with a unique mechanism of action. They have proved to be useful for hypertension and congestive heart failure (Parish & Miller, 1992: 15). ACE inhibitors are also indicated for the co-treatment of many disorders including myocardial infarction, asymptomatic left ventricular dysfunction, and diabetic nephropathy. They form a heterogenous group of agents, and important pharmacologic, pharmacokinetic, and therapeutic differences among them must be understood to obtain optimal therapy (White, 1998: 588).

These agents interfere with an enzyme that converts angiotensin I into angiotensin II (one of the most powerful blood vessel constricting substances in the body). Narrowed blood vessels in the kidney increase blood pressure. Angiotensin II also stimulates the secretion of aldosterone, a hormone that produces salt and water retention, causing blood pressure elevation (Wood & Griffith, 1997: 199).

In treating hypertension the ACE inhibitors are as efficient as all the other antihypertensive drugs. They are well tolerated and cause no reduction in quality of life. It is proposed that possible antihypertensive mechanisms of ACE inhibitors include the following:

- Reduction in circulating angiotensin II levels.
- Inhibition of local synthesis of angiotensin II in vascular tissue.
- Attenuation of norepinephrine release from peripheral sympathetic nerve endings.
- Augmentation of formation of bradykinin and vasodilatory prostaglandins.
- Increase of sodium excretion by reducing aldosterone secretion and increasing renal blood flow (Shionoiri, 1993: 22).

ACE inhibitors reduce systemic blood pressure in patients with essential, renovascular and renal hypertension (Shionoiri, 1993: 22). Unlike most other vasodilator drugs, ACE inhibitors lower blood pressure without inducing an increase in heart rate. This may be due to blunting of sympathetic reflex responses by ACE inhibitors. White patients tend to respond better than blacks but differences in age are of no practical significance (Freis & Papademetriou, 1996: 5).

2.2.3. Mechanism of action

The first mechanism:

The ACE inhibitors were developed to block the effects of the renin-angiotensin system. Renin, an enzyme released from the kidney in the juxtaglomerular cells of the afferent renal arterioles, converts angiotensin to the essentially inactive decapeptide, angiotensin I. A converting enzyme, found chiefly in the lungs but also in numerous other tissues, acts on the octapeptide, angiotensin II. This octapeptide has two principal blood pressure- raising actions. First it exerts a powerful direct vasoconstrictor effect on the arterial circulation by stimulating G protein-coupled angiotensin II type 1 receptors in the arterioles to elicit a negative feedback for renin

release and to cause increased tubular reabsorption of sodium (via aldosterone), efferent arterioles of the kidneys to cause vasoconstriction, brain to cause thirst and release of antidiuretic hormone, sympathetic nervous system to increase activity, and heart to cause mitogenesis and increased contractility. Second the angiotensin II type 2 receptors are not G protein linked and their function is not known. ACE inhibitors prevent conversion of angiotensin I to angiotensin II by ACE (White, 1998: 588-589).

The second mechanism:

This mechanism was produced by Zusman and may also be important. The angiotensin converting enzyme, known as kininase II, is also responsible for the degradation of the vasodilative substance bradykinin to its inactive products (Weber & Zusman, 1986: 43). ACE inhibitors inhibit the metabolic degradation of the kinins, including bradykinin (Freis & Papademetriou, 1996: 5). Thus in theory, the ACE inhibitors could lower blood pressure partly by increasing plasma concentration of kinins. Although the direct importance of this effect in lowering blood pressure has not been established, it may be that a secondary action of the kinins, the stimulation of intrarenal prostaglandins, plays a role (Weber & Zusman, 1986:43).

The most practical explanation for this second mechanism is that ACE inhibitors 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 (PGE_2 and PGI_2), which may contribute to the positive haemodynamic effects of the ACE inhibitors. ACE inhibitors also reduce the activity of the sympathetic nervous system since angiotensin II promotes the release of noradrenaline and inhibits its reuptake. In addition they also improve beta-receptor density causing their up regulation, variation in heart rate, baroreceptor function, and autonomic function including vagal tone (Davies *et al.*, 2000: 429).

Although converting enzyme inhibitors are most effective in conditions associated with high plasma renin activity, there is no good correlation among subjects between plasma renin activity and antihypertensive response. Accordingly, renin profiling is unnecessary. ACE inhibitors have a particularly useful role in treating patients with diabetic nephropathy, diminishing proteinuria and stabilising renal function (even in the absence of lowering of blood pressure). These benefits probably result from improved intrarenal hemodynamics, with decreased glumerularefferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure (Katzung, 1998: 207).

2.2.4. Classification and actions of ACE inhibitors

According to Mignat and Unger (1995: 335) ACE inhibitors have in common a moiety that can bind with the zinc ion located in the active site on the ACE. The chemical structure of the zinc binding ligand serves as criterion for dividing the ACE inhibitors into 3 classes based on the chemical structure of drugs containing ACE inhibitors:

- The *Carboxyl-containing ACE inhibitors* (e.g. Enalapril)
- The *Sulphydryl* (e.g. Captropil) and
- The *Phosphinyl* (e.g. Fosenopril)

Despite these structural differences, all ACE inhibitors share an essentially similar qualitative pharmacodynamic profile which is related to their key action in inhibiting ACE, an important component of the renin-angiotensin-aldosterone system (Mignat & Unger, 1995: 335).

For the purpose of this study, the ACE inhibitors were divided into the following classes:

TABLE 2.1.Classification of ACE inhibitors.

Carboxyl	Sulphydril	Phosphonyl	Combination with other drugs
Benazepril	Captopril	Fosenopril	Benazepril + Hydrochlorothiazide
Cilazapril			Captopril + Hydrochlorothiazide
Enalapril			Cilazapril + Hydrochlorothiazide
Lisinopril			Enalapril + Hydrochlorothiazide
Perindopril			Lisinopril + Hydrochlorothiazide
Quinalapril			Fosenopril + Hydrochlorothiazide
Ramipril			Perindopril + Indapamide
Trandolapril			Quinalapril + Hydrochlorothiazide
			Ramipril + Felodipine
			Trandolapril + Verapamil hydrochloride

(On classifying the ACE inhibitors, a fourth category had to be included as the product combination of ACE inhibitors and other drugs as they appeared in the database. This combination group will be analysed as an individual class of ACE inhibitors).

ACE inhibitors differ in functional group, whether they are administered as prodrug, their availability in oral and intravenous forms, lipophilicity and tissue penetration, elimination route, onset and duration of action, trough : peak blood pressure ratio, dialyzability, and amount of information available for certain disease states (White, 1998: 596). All of the available ACE inhibitors have demonstrated efficacy for the management of hypertension namely: benazepril, captropil, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril and trandolapril (Piepho, 2000: s6, 27).

In general, ACE inhibitors may differ with regard to their properties according to their classification (refer to table 2.2) as follows:

- Potency.
- Whether ACE inhibition is due primarily to the drug itself or to conversion of a prodrug to an active metabolite.
- Pharmacokinetics (i.e. extent of absorption, effect of food on absorption, plasma half-life, tissue distribution, and mechanisms of elimination) (Kelly & Smith, 2001: 821).

TABLE 2.2. ACE inhibitors currently available and in development (DeFelice & Kostis, 1987)

Ligand	Pro-drug	Bio-availability (%)	T_{max}(h)	Plasma half-life(h)	Mode of excretion	Duration of ACE inhibition	Duration of anti-hypertensive effect	Estimated daily dose(mg)	Comments
Sulfhydryl									
Captopril	No	70	0.5-1.5	2	Renal	S	S	25-150	
Carboxyl									
Benazepril	Yes	37	0.5-1	11	Renal	L	L	5-80	
Cilazapril	Yes Yes	52	1.0	1.5-2.0	Gut/Renal	L	L	5-20	
Enalapril	No	40	1.0	11	Renal	L	L	2.5-40	
Lisinopril	Yes	25	7.0	12.6	Renal	L	L	10-80	
Perindopril	Yes		8.0			L	L	4-8	
Quinapril	Yes	75-80	1.5	2-3	Hepatic	L	L	5-20	
Ramipril	Yes	54-65	0.3-1.0	11-27	Renal	L	L	2.5-10	Similar potency to enalapril
Trandolapine		70	4-10	10	Renal/hepatic	L	L	1-8	
Phosphinyl	Yes								
Fosenopril		25-29[a]	2.4-4.2[a]	15[b]	Hepatic/gut/ renal	L	L	10-160	

[a] diacid.

[b] elimination half-life.

Abbreviations: t_{max} = time required to achieve maximum blood concentration; L = long-acting (≥24h); S = short-acting (<12h); I = intermediate action (12-24h).

2.2.5. Pharmacokinetic classification

According to Opie (1992: 149;152), there are three types of ACE inhibitors from the pharmacokinetic point of view.

- The *captopril like*, already in the active form, yet undergoes further metabolism. Such metabolic conversion produces disulphides with pharmacological activity. Both the parent compound and the disulphides are eliminated by the kidney.
- The *prodrugs*, for example, enalapril which becomes active only on conversion to enalaprilat, which occurs chiefly in the liver. This diacid form can then either be eliminated in the kidneys or may be taken up into the tissues where it is thought inhibition of tissue ACE activity may occur. Examples of such prodrugs include benazepril, cilazapril, perindopril, quinapril and ramipril.
- The *water soluble*, compounds which do not undergo metabolism. Lisinopril is the prototype. Such compounds do not need any further metabolic conversion to be activated. They circulate unbound in plasma protein and undergo renal elimination in the unchanged form. The only determinants of the plasma level are, therefore, the oral dose, the rate of absorption, and the rate of renal excretion.

2.2.5.1. ACE inhibitors according to their different classifications (refer to table 2.1)

Carboxyl group:

- **Benazepril**

Benazepril, a prodrug, is converted to benazeprilat chiefly by hepatic metabolism in the liver. It has a plasma protein binding of 95%-97%. After oral administration the active metabolite, benazeprilat, starts to appear in the blood within 30 minutes and reaches peak values after 1 hour. It appears to be well tolerated with no evidence for an incidence of side effects any different from that of other ACE inhibitors. It is then excreted by the kidneys (Opie, 1992: 154;155).

- **Cilazapril**

Cilazapril is a prodrug, being converted to cilazaprilat. It is rapidly absorbed and reaches peak values in an hour. It is then metabolised by de-esterification to its active form in the liver and blood. Cilazapril exerts a long lasting (up to 24 hours) inhibition of serum ACE activity without drug accumulation on repeated administration. Its plasma protein binding is unknown (Salvetti, 1990: 805;806). Both cilazapril and cilazaprilat are found in the urine following dosage of the compound to patients. Almost all the cilazapril is excreted by 6 to 8 hours, whereas there is progressive excretion of cilazaprilat in two phases, first an early phase and then a later phase from approximately 8 to 24 hours of much slower excretion (Opie, 1992: 155;156).

- **Enalapril**

Enalapril maleate, the second inhibitor approved, is a prodrug that is highly active and must be hydrolysed by esterases in the liver to produce the active parent dicarboxylic acid, enalaprilat. It is rapidly absorbed when given orally and has an oral bioavailability of about 60%. The peak values in plasma occur within an hour. Enalapril has a plasma protein binding of less than 50%. Absorption of enalapril is not reduced by food. Nearly all the drug is eliminated by the kidneys either as intact enalapril or enalaprilat (Kelly & Smith, 2001: 821).

- **Lisinopril**

Lisinopril is thus far the only clinically available representative of the type of ACE inhibitor not metabolised, but water-soluble. It is itself active and slowly, variably and incompletely (30%) absorbed after oral administration. Lisinopril reaches peak plasma concentration about 7 hours after administration. Lisinopril is not at all protein bound and is entirely water-soluble. Lisinopril does not accumulate in the tissues and its absorption is not reduced by food. Since lisinopril is not metabolised, it is excreted as an intact compound by the kidneys (Kelly & Smith, 2001: 821).

- **Perindopril**

Perindopril is an ester prodrug which is hydrolysed to its active form, perindoprilat which is twice as potent. Perindopril is extensively absorbed ranging between 60% and 80% and has a peak plasma value of 3 hours. It has a protein binding of 20% and does not accumulate in the tissues nor is its absorption reduced by food. The major elimination of perindopril is by metabolic conversion, with renal excretion playing a part. The active drug is eliminated mainly by the kidney (Salvetti, 1990: 810,811).

- **Quinapril**

Quinapril is a prodrug that becomes active by conversion to its metabolite, quinaprilat in the liver. It is highly lipophilic, which may have some advantage for tissue penetration and effects on the tissue renin-angiotensin system. Quinapril is rapidly absorbed and its absorption is not influenced by food intake. It reaches its peak plasma value within 1 hour. It is highly protein bound, about 97%. It differs from the other carboxy diacids in that it has a very short half-life. It is excreted by the kidney (Opie, 992: 155;156).

- **Ramipril**

Ramipril, a mono-ethyl ester prodrug, is converted to active diacid compound, ramiprilat, which binds completely with ACE, initially forming an enzyme inhibitor complex with a slow rate of dissosiation. Ramipril is rapidly absorbed and extensively metabolised, probably in the liver. Ramipril and ramiprilat are bound to human serum proteins, 73% and 56% respectively. It is excreted chiefly by the kidneys and to a lesser extent in the feces (Salvetti, 1990: 810;811).

- **Trandolapril**

Trandolapril is converted to the active form, trandolaprilat which is on average 8 times more potent than other ACE inhibitors. After fast absorption and high first pass metabolism, trandolaprilat is rapidly formed. Its binding depends on the concentration, being 94% at low concentrations and 80% at higher concentrations (Opie, 1992: 155;156).

Absorption rate but not extent is reduced by food. The plasma peak concentration of trandolapril is 4 to 10 hours. It displays biphasic elimination kinetics, being eliminated in urine (33%) and in the feces (66%) (Salvetti, 1990: 810,811).

Sulphydril group:

- **Captopril**

Captopril is the first of the ACE inhibitors to be approved for use, that contains a Sulphydril moiety. It is already in the active form and does not require metabolic conversion. Given orally, captopril is readily absorbed and reaches its peak value within an hour. Food reduces its oral bioavailability by 25% to 30% so the drug should be given 1 hour before meals (Kelly & Smith; 2001:821). It has a plasma protein binding of 30% and is partially metabolised in the liver and in blood, to the disulfide form and to polar metabolites. About two thirds of an oral single dose is excreted within four hours in the urine, either unchanged or converted to polar metabolites. Within 24 hours 95% of the oral dose is excreted, either unchanged or as metabolites (Opie, 1992: 155;156).

Phosphonyl group:

- **Fosenopril**

Fosenopril, an ester prodrug, is converted mainly in the gastrointerstinal mucosa and in the liver, to its active form, fosenoprilat. It is slowly absorbed and extensively and rapidly converted. It reaches its peak plasma concentration in about 3 hours. It is long acting, highly protein bound and cleared slowly from the body. It has dual routes of excretion, hepatic and renal (Salvetti, 1990:810;811).

2.2.6. Side effects (major side effects)

Opie (1992: 194-201) stated that, ACE inhibitors are regarded as a rather safe category of drugs with occasional side effects:

- Angioedema, although a rare reaction, when it does occur, can be near fatal. It usually follows the first dose or else develops within 48 hours of starting therapy.
- Cough is probably the most common and irritating side effect of ACE inhibitors but not all patients are susceptible. It sometimes appears at the start of therapy and sometimes later on.
- Hypotension, a feared complication of ACE inhibitor therapy, can occur in both patients with congestive heart failure or severe hypertension.
- Temporary exaggeration of renal failure may occur. Renal failure as a class effect of ACE inhibitors is completely different from captopril-induced kidney damage.
- Hyperkalemia may occur, because ACE inhibitors act to inhibit the release of aldosterone, they tend to increase plasma potassium. Hence, combination with potassium supplement therapy or potassium containing diuretics may lead to hyperkalemia.

2.2.7. Drug interactions

Certain drug interactions have been reported with all ACE inhibitors.

- When combined with diuretics, ACE inhibitors are more likely to cause hypotension;
- hyperkalaemia is common in conjunction with potassium-sparing diuretics;
- nonsteroidal anti-inflammatory drugs may blunt the antihypertensive efficacy of ACE inhibitors by increasing sodium and water retention (Gerbrandt & Yedinak, 1996: 607).

2.2.8. Contraindications to ACE inhibitor therapy

The contraindications to ACE inhibitor therapy include bilateral renal artery stenosis, unilateral renal artery stenosis in a solitary kidney, significant aortic stenosis, severe obstructive cardiomyopathy, and pregnancy or risk thereof. Preexisting chronic cough is a relative contraindication (Opie, 1992: 201).

2.2.9. Clinical efficacy

ACE inhibitors have produced physiological benefits in the management of patients with hypertension and survival benefit in patients with congestive heart failure. Thou all ACE inhibitors are used for the treatment of hypertension, not all are used for congestive heart failure (Anon, 2002b: 1).

2.3. HYPERTENSION

2.3.1. Definition of Hypertension

As blood flows from the heart to the blood vessels, it creates pressure against the blood vessel walls. Your blood pressure reading is a measure of this pressure. When that reading goes above a certain point, it is called hypertension. Hypertension is another name for elevated blood pressure or high blood pressure (HBP). It is a serious condition that can lead to stroke, heart disease, kidney failure, and other health problems (Anon, 2002b: 1).

A high diastolic blood pressure has commonly been used to define hypertension. This arbitrary choice was based on the fact that diastolic blood pressure was used as the criterion for the inclusion in most randomised therapeutic trials, including those on mild hypertension. However, systolic values are as important as the cardiovascular risk is as strongly associated with systolic as with diastolic values, with no evidence of a threshold below which a decrease in systolic pressure does not reduce risk (WHO, 1996:4).

The average blood pressure reading for adults is 120/80mm Hg, systolic/diastolic. A slightly higher or lower reading may not be a problem. If blood pressure goes above 140/90mm Hg, however, some form of treatment diet or drugs may be needed. Lower blood pressure readings (for example, 110/70mm Hg) are thought to be safe for most people. Often in adults the first number (the upper or systolic) measure is high while the second (the lower or diastolic) measure is normal, e.g. 180/80mmHg or 160/80 mmHg. This condition is called isolated systolic hypertension, and it also should be treated (refer to paragraph 2.3.6). Studies prove that lowering the systolic blood pressure cuts down on stroke and heart attack in people aged 60 and over (Anon, 2002c: 1).

In both young and older adults the blood pressure increase with age is largely determined by the initial blood pressure levels. However, in connection with aging, isolated systolic hypertension deserves special consideration. It may be viewed as a concomitant of aging, being quite infrequent until the mid-fifties, rising further with advancing age and carrying an increase in the risk of cardiovascular disease (WHO, 1983: 10).

However, absolute blood pressure levels vary with sex, age, race, and numerous other factors. The rate of progression of hypertension varies from one individual to another depending on the genetic and environmental background (WHO, 1978: 8).

Fifty million Americans have elevated blood pressure. Of these, 68% are aware of their diagnosis, 53% are receiving treatment, and only 27% are under control by the 140/90mm Hg threshold. The proportion of individuals who are hypertensive with age is greater in blacks than in whites, but because blood pressure readings in many individuals are highly variable-especially in the office setting, the diagnosis of hypertension should be made only after elevation is noted on three readings on different occasions, over a period of several months unless the elevations are severe or associated with symptoms (Massie, 2000: 448).

Today extensive epidemiological studies in Africa, south of the equator, have shown that, high blood pressure is the most common cardiovascular ailment in Africa and that one in four African patients with heart failure suffers from the condition. Next to violence and accidents, high blood pressure and its complications are alleged to be the most common cause of death among adult blacks on the Witwatersrand. Among Indians of South Africa, data from the Department of Statistics have shown that heart attack, mainly in males and 'strokes' mainly in females as a result of high blood pressure are the commonest causes of death (Seedat, 1980: 2).

2.3.2. Classification of hypertension

The purpose of a classification of hypertension is to provide an easy and reliable method for the classification of each patient. It allows assessment of severity of disease by reference to epidemiological data so that the risk can be defined and appropriate treatment instituted (WHO, 1978: 8).

Classification of hypertension based on epidemiological, observational and interventional data, and taking into consideration associated risk factors and development of hypertension-related organ damage, provides an easy and reliable method of assessing risk and the most appropriate treatment for each patient. With the obvious warning that all classifications of hypertension are based on arbitrary choices, arterial hypertension may be classified in three ways, namely: blood pressure, extent of damage to the organs and etiology (WHO, 1996: 7).

BLOOD PRESSURE LEVEL

It is emphasized that there is no clear demarcation between " normal " and " hypertensive" blood pressure levels. In epidemiological studies casual blood pressure measurements should be reported in the form of distribution curves and age-specific means (WHO, 1978a: 8). The predictive value of one of casual blood pressure measurements has been demonstrated in a number of epidemiological studies, but it is recommended that for the clinical classification of hypertension at least three blood pressure readings be taken on at least two different occasions, except in emergencies (WHO, 1978: 8).

EXTENT OF ORGAN DAMAGE

Although the extent of organ damage often correlates with the level of blood pressure, it is not always the case. In addition the rate of progression of organ damage varies from one individual to another depending on many influences, most of which are incompletely understood. Therefore, blood pressure and organ impairment should be evaluated separately, since markedly high pressures may be seen without organ damage and, conversely, organ damage may be present with only moderate elevation of blood pressure. The presence of signs of organ damage confers an increased cardiovascular risk to any level of blood pressure (WHO, 1996: 8).

The classification of hypertension by extent of organ damage uses stages to indicate progression of the severity of disease with time (WHO, 1996: 9).

Stage I:

No objective signs of organic damage are observed.

Stage II:

At least one of the following signs of organ involvement is present:

- Left ventricular hypertrophy on physical examination, chest X-ray, electrocardiography, echocardiography, etc.
- Generalised and focal narrowing of the retinal arteries.
- Proteinuria and/or slight elevation of plasma creatinine concentration.

Stage III:

Both symptoms and signs have appeared as a result of damage to various organs from hypertensive disease. These include the following:

- Heart: left ventricular failure.
- Brain: cerebral, or brain stem haemorrage; hypersensitive encephalopathy.
- Optical fundi: retinal haemorrhage and exudates with or without papilloedema. These features are pathognomonic of the malignant (accelerated) phase.

Other conditions frequently present in stage III but less clearly a direct consequence of hypertension include the following:

- Heart: angina pectoris; myocardial infarction.
- Brain: intracranial arterial thrombosis.
- Vessels: dissecting aneurysm; arterial occlusive disease.
- Kidney: renal failure.

ETIOLOGY

Essential or primary hypertension:

This is defined as a high blood pressure without evident organic cause. Here, the person has high blood pressure but the cause is not known and can not be defined (WHO, 1978:9).

Secondary hypertension:

This is defined as hypertension with identifiable causes. The possible causes are classified below.

I. Hypertension due to the administration of drugs.

- Hormonal contraceptive.
- Licorice and carbenoxolone.
- Adrenocorticotropic hormone and corticosteroids.

II. Hypertension disease of pregnancy.

-Most people develop hypertension during pregnancy.

III. Organic disease

-Coarctation of the aorta.

-Renal disease (renal artery stenosis, glomerulonephritis, pyelonephritis, radiation nephritis, renal tuberculosis, renal cysts, hydronephrosis, renal tumors, including renin-secreting tumors and renal failure) (WHO, 1978: 9-10).

2.3.3. Causes of Hypertension

Some cases of hypertension are caused by illnesses. This kind of hypertension is called secondary hypertension, and it is often cured once the original medical problem is cured. Most cases of high blood pressure, however, are classified as essential or primary hypertension. This kind cannot be cured but can be kept under control by regular, ongoing treatment (Anon, 2002a:2).

Health professionals are of the opinion that many things combine to cause high blood pressure. Being overweight, drinking too much alcohol, and eating too much salt are risk factors because they raise your risk of having high blood pressure (HBP). They do not cause it directly (Anon, 2002a:2).

Blood pressure goes up in all people during periods of stress or exercise, but avoiding stress will not prevent HBP. You can have HBP even though you are usually a calm, relaxed person (Anon, 2002a:2).

2.3.4. Hypertension and pathophysiology

Untreated hypertension affects many organs. In order to compensate for the increased pressure against which it has to work the left ventricle of the heart increases in size by increasing the thickness of its wall. This ultimately leads to congestive heart failure. Along with this there is increased atherosclerosis leading to hypertension, resulting from the heart attack or cardiac failure (Anon, 2002b: 53).

The nervous system is affected in many ways. The vessels of the retina provide an excellent way of seeing the effect of hypertension on the blood vessels directly. They are examined in a hypertensive patient to get some measure of the effects of treatment. Atherosclerosis of these vessels can lead to problems with vision and even blindness in poorly controlled or undiagnosed hypertension.

Mild nervous system effects such as headache, dizziness and light-headedness can occasionally be seen, but these are relatively uncommon. The most serious neurological event that can result from poorly controlled high blood pressure is stroke. This may be as a result of atherosclerosis causing a blockage in a cerebral vessel, or hemorrhage resulting from weakening of the arteries of the brain due to raised blood pressure.

The kidneys are the other organs most commonly affected by hypertension, and poorly controlled hypertension can often lead to kidney failure (Anon, 2002b: 53).

2.3.5. Prevention of hypertension

The aim of primary prevention of hypertension may thus be expressed in both of the following ways, which are regarded as complementary:

- In the high risk individual, to the attainment of levels of blood pressure at which the institution of management and treatment would be considered.

- In the general population, to delay or arrest further progression of blood pressure levels beyond those attained upon reaching adulthood (WHO, 1983: 8).

There is now good evidence that HBP can be prevented in many people. The keys to prevention are

- keeping your weight moderate;
- cutting down on salt;
- exercising regularly; and
- having no more than two alcoholic drinks a day (WHO, 1996: 10).

HBP checklist

- HBP may not make you feel sick, but it is serious and should be treated by a doctor.
- You can bring down your blood pressure with changes in diet and daily habits and by taking medicines if necessary.
- Losing weight, cutting down on salt and alcohol, and getting regular exercise may be helpful, but only as suggested by your doctor. Do not assume these are substitutes for medicine unless your doctor says they are (Anon, 2002a:3).

In summary, the need for primary prevention is clear. For prevention to have an adequate impact on the population, both the high risk and mass strategy must be implemented (WHO, 1983: 8).

2.3.6. Management of hypertension

In general, most patients with chronic hypertension have no identifiable cause for the disease. Treatment usually involves drug therapy, and this commits the patient and the physician to a long-term association. Prior to the institution of an antihypertensive regimen, however, general therapeutic measures are necessary (WHO, 1978: 34).

2.3.6.1. General measures

Attention to matters affecting the general health is always advisable with a chronic illness. These include weight reduction, cessation of smoking, and moderation in alcohol ingestion. Rigid salt restriction has been demonstrated to be effective in lowering blood pressure but is not practicable in everyday life (WHO, 1978: 34).

Certain measures may also contribute to the lowering of blood pressure:

Lifestyle measures that contribute to lowering blood pressure:

- Weight reduction.
- Reduction of alcohol.
- Increased physical activity.
- Moderation of dietary sodium.

Lifestyle measures for the treatment of associated risk factors:

- Cessation of tobacco smoking
- Reduced fat intake
- Control of diabetes (WHO, 1996: 55).

Different management strategies or plans can be used to help in the easy management of hypertension:

Management plan:

According to WHO (1996: 60-61) the management of hypertension may be divided into four phases, namely:

Mild hypertension

The decision to treat should be based not only on the diastolic and the systolic blood pressures but also on the total cardiovascular risk in the individual patient.

Moderate and severe hypertension

Patients presenting with average Diastolic blood pressure of 105-120 mmHg and/or Systolic blood pressure of 180-210 mmHg should be referred for immediate evaluation and assessed carefully for target organ damage, associated cardiovascular risk factors and history of previous antihypertensive therapy.

Resistant hypertension

Patients who continue to have moderate to severe HBP after therapies for at least one month have resistant hypertension. Excess salt and alcohol intakes are other causes of resistance to therapy; and the "white coat effect" (where a patient's blood pressure only becomes elevated in the presence of a doctor or a nurse) can cause apparent resistance (WHO, 1978: 34).

Hypertensive emergencies

The following conditions need rapid reduction of blood pressure and require admittance to the hospital with immediate intervention: severe hypertension with papilloedema or haemorrage in the optic fundus (malignant and accelerated hypertension), hypertension complicated by acute left ventricular failure, cerebrovascular accident, acute coronary event, acute aotic dissection, hypertensive encephalopathy, hypertensive crisis of phaeochromacytoma, eclampsia, and hypertension following cardiac surgery or due to a food or drug interaction with a monoamine oxidase inhibitor.

2.3.6.2. Withdrawal of a drug responsible for hypertension

The majority of patients respond to the withdrawal of drugs that cause hypertension, but those patients whose blood pressure remains high require evaluation and antihypertensive treatment (WHO, 1978: 34).

2.3.6.3. Surgical treatment

For a variety of reasons surgery may not always be indicated. Only in some cases will blood pressure reach a normal level after the operation has been performed. Careful follow-up is necessary and institution of drug therapy may be required (WHO, 1978: 34).

2.3.6.4. Drug treatment

The objective of antihypertensive therapy is to prevent the morbidity and mortality related to this condition (Massie, 2001: 455). Hypertension is common and there is a bewildering array of drugs used in its treatment. The exact type of treatment will depend on the individual, his or her general practitioner (GP), and which drugs the GP has the most experience of and faith in (Anon, 2002b:55).

Drug treatment is needed for the great majority of patients with essential hypertension and also for those in whom pressure does not fall to normal after correction of any identifiable cause. Effective hypertension treatment in adults can be regarded arbitrarily as maintained reduction of the casual blood pressure to 140/90 mmHg or below, although treatment may be beneficial with less marked lowering of pressure. In most cases it will not be necessary to reduce blood pressure rapidly.

It should be borne in mind that there are wide regional and national differences in the availability of drugs and in the kind of drugs most favoured (WHO, 1978: 35). There are at present eight to ten different classes of antihypertensive drugs (Massie, 2001: 456).

There is general agreement that five classes of drugs are most suitable for the first line treatment of patients with hypertension. They are the diuretic, the beta-blockers, the ACE inhibitors, the calcium antagonists and the alpha-blockers (WHO, 1996: 55). Each of these drugs acts differently and has its onset of side effects (Anon, 2002b:55). The general principle is to begin treatment with an antihypertensive agent that may achieve only a modest reduction in pressure but which has relatively minor side effects (WHO, 1978: 35).

Sometimes two drug types will combine in a single drug, with the aim of increasing patient compliance (Anon, 2002b:55). The regimen progresses only to combinations of drugs if the

simpler methods fail (WHO, 1978: 35), but most academic pharmacologists caution against combined preparations as their actions are not as predictable as the single drug preparation (Anon, 2002b:55).

The administration of two, three, or even more drugs with different mechanisms of action may be necessary to obtain control of blood pressure. The progressive addition of drugs in this scheme should be stepwise and systematic. In patients with severe hypertension, however, it may be advisable to start with a combined therapy, from which components may be withdrawn later when control of high blood pressure has been achieved (WHO, 1978: 35).

A number of considerations enter into the selection of the initial drug for a given patient. These include the weight of evidence for beneficial effects on clinical outcomes, the safety and the tolerability of the drug, its cost, demographic differences in response, concomitant medical conditions, and lifestyle issues (Massie, 2001: 456).

The specific classes of antihypertensive medications are discussed below; here the treatment that was used in the 1970s by WHO was compared to the treatment protocol prescribed by Snyman (2002: 134):

- The drugs most widely used for initial treatment are the thiazide and related diuretics or beta adrenoreceptor blocking agents (beta-blockers).
- In the second step, if necessary, these two agents may be prescribed in combination, or either of them may be combined with other antihypertensive drugs such as reserpine, methyldopa, hydralazine, or prozosin.
- In the third step, three of the above quoted drugs are given simultaneously, leading to combinations such as: diuretic + beta blocker + hydralazin, or diuretic + beta blocker + prazosin, or diuretic + reserpine + hydralazine.
- In the fourth step still another potent drug such as guanethidine, betanidine, debrisoquine, or minoxidil may be added to any of the above (WHO, 1978: 35).

As treatments change with the times, Snyman (2002: 134) developed a new hypertension treatment of initial drug choices:

Initial drug choices, unless contra-indicated (*Based on randomised controlled trials)*

Uncomplicated hypertension

- Diuretics.
- Beta-blockers.

Compelling indications

- Diabetes mellitus (type 1) with proteinuria – ACE inhibitor.
- Heart failure – ACE inhibitors and Diuretics.
- Isolated systolic hypertension – Diuretic.
- Myocardial infarction – Beta-blockers and ACE inhibitors.

The six fist-line classes of antihypertensive medications are discussed below according to the use as first line drugs to the last, and guidelines for selecting the first-line drugs for hypertension are offered thereafter:

➢ **Diuretics**

Diuretics are the antihypertensive drugs that have been most extensively studied and most consistently effective in clinical trials. Diuretics lower blood pressure initially by decreasing plasma volume (by suppressing tubular reabsorption of sodium, thus increasing the excretion of sodium and water) and cardiac output, but during chronic therapy their major hemodynamic effect is reduction of peripheral vascular resistance (Massie, 2001: 456).

Diuretics have been widely used as the first-line drug in the treatment of hypertension and have been shown to prevent cardiovascular morbidity and mortality, especially fatal and non-fatal stroke (WHO, 1996: 55).

The drug of first choice is still one of the long-acting thiazides or related diuretic compounds (i.e. hydrochlorothiazide, chlorthalidone, metolazone) provided that the patient has a good renal function (serum creatinine less than 2.5 mg/100 ml) and does not have an overt maturity-onsert diabetes mellitus controlled with diet or oral hypoglycemic agents, in which case thiazides may

increase hyperglycemia. In patients with most advanced renal insufficiency, metolazone is still effective, as it does not reduce the glomerular filtration rate and has the advantage of smooth long-lasting action over the more commonly used furosemide (Rosenthal & Silverberg, 1987: 63).

Most of the antihypertensive effect of these agents is achieved at lower dosages (typically 12.5 or 25 mg of hydrochlorothiazide or equivalent), but their biochemical effects are dose-related (Massie, 2001: 456). Particularly in large doses, diuretics may cause a variety of unwanted metabolic effects – principally potassium depletion, reduced glucose tolerance, ventricular ectopic beats and impotence. These can be reduced by keeping the dose as low as possible. Low-dose diuretics remain effective, not only in lowering elevated blood pressure, but also in reducing cardiovascular morbidity and mortality (WHO, 1996: 55).

During chronic therapy, hydrochlorothiazide may be administered every other day with undiminished efficacy. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short duration of action; therefore they should not be used in the treatment of hypertension except in the presence of renal dysfunction.

Relative to the beta-blockers and ACE inhibitors, diuretics are more potent in blacks, older individuals, the obese, and other subgroups with increased plasma volume or low plasma renin activity. Interestingly they are more effective in smokers than in non-smokers. Overall diuretic administration alone controls blood pressure in 50% of patients and can be used effectively in combination with all other drugs (Massie, 2001: 456).

Diuretics are particularly valuable as ancillary treatment to enhance the effectiveness of many other types of antihypertensive drugs. Diuretics are also inexpensive (WHO, 1996: 55).

THE SIDE EFFECTS:

- Hypokalemia – especially in digitalised patients - with the attendant risk of myocardial irritability and digitalised toxicity (Rosenthal & Silverberg; 1987: 63). A combination of diuretics with potassium-sparing drugs or ACE inhibitors may prevent potassium depletion (WHO, 1996: 55).

- Hyperuricemia, which does not need specific treatment unless it exceeds 10-12 mg/100 ml, except in patients with prior history of gout who need additional treatment with other uricosuric-or urate-suppressing agents to offset this side effect of thiazides.
- Hypercalcemia, particularly in immobilised patients. Caution must also be exercised when potassium-sparing diuretics such as spironolactone or triamterene or potassium chloride supplements are added to correct hypokalemia, since patients with some degree of renal insufficiency are at risk of developing hyperkalemia.

In addition, excessive diuresis can cause dehydration leading to orthostatic hypotension to which older individuals are particularly vulnerable, as well as to prerenal azotemia, which may be mistaken as an irreversible deterioration of the renal status (Rosenthal & Silverberg, 1987: 63).

THE ADVERSE EFFECTS:

The adverse effects of diuretics relate chiefly to the metabolic changes, though, impotence, skin rashes and photosensitivity are less frequent side effects (Rosenthal & Silverberg, 1987: 64).

➢ **Beta-adrenegic blockers**

Beta-adrenergic receptor antagonists are becoming increasingly the drug of choice to add when a diuretic is not sufficient to maintain blood pressure (Rosenthal & Silverberg, 1987: 64). They are widely used in subjects of all ages with hypertension of all degrees of severity. They have been part of the treatment regimen in many of the major studies that have demonstrated reduction in morbidity and mortality attributed to lowering blood pressure (WHO, 1996: 55).

A large variety of beta-blockers are available (propranolol, atenolol, metoprolol, nadolol, acebutolol hydrochloride (HCL), pindolol, timolol maleate, penbutolol sulfate, cartelol HCL, bisoprolol fumarate and betaxol HCL). Some are cardio-selective, i.e. they work selectively on the heart while others demonstrate some intrinsic sympathomimetic activity or have vasodilator properties (WHO, 1996:55). These drugs are effective in hypertension because they decrease the heart rate and cardiac output. Even after continued use of beta-blockers, cardiac output remains lower and systemic vascular resistance higher with agents that do not have intrinsic sympathomimetic or alpha-blocking activity (Massie, 2001: 458).

Beta-blockers decrease renin release and are more efficacious in populations with elevated plasma renin activity such as younger white patients. They neutralise the reflex tachycardia caused by vasodilators and are especially useful in patients with associated condition that benefit from this therapy. These include individuals with angina pectoris, previous myocardial infarction, stable congenital heart failure and those with migraine headaches and somatic manifestation of anxiety (Massie, 2001: 458).

Beta-blockers have shown to be useful in the secondary prevention of myocardial infarction, they have not been shown to have any advantage over diuretics in the primary prevention of myocardial infarction in hypertensive patients (WHO, 1996: 55).

Although all beta-blockers appear to be similar in antihypertensive potency, controlling approximately 50% of patients, they differ in a number of pharmaceutical properties. They also differ in their pharmacokinetic and lipid solubility, which determines whether they cross the blood brain barrier and affect the incidence of central nervous system side effects and route of metabolism (Massie, 2001: 458).

THE SIDE EFFECTS:

- Inducing or exacerbating bronchospasm in predisposed patients, e.g. asthmatics and some chronic obstructive pulmonary disease (COPD) patients.
- Sinus node and atrioventricular conduction depression resulting in bradycardia or atrio ventricular (AV) block.
- Precipitating or worsening left ventricular failure, although recommended for stable patients with underlying left ventricular systolic dysfunction.
- Nasal congestion.
- Raynaud's phenomenon, especially in women.
- Central nervous system symptoms with nightmares, excitement, depression, and confusion.
- Fatigue, lethargy and impotence may occur (Massie, 2001: 458) and (WHO, 1987: 64).

THE CONTRAINDICATIONS:

There are a number of contraindications in the use of beta-blockers:

- Patients with congestive heart failure.
- Patients with type 1 diabetes mellitus, they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeogenesis.
- Patients with chronic obstructive airway disease as they can precipitate severe broncho-constriction.
- Should be used with caution in patients with advanced peripheral vascular disease associated with rest pain (i.e. pain when you are lying down) or non-healing ulcers

(Massie, 2001: 458) and (WHO, 1987: 64).

THE ADVANTAGES:

- They lack orthostatic hypotension.
- They have a minimal potential for central nervous system depression.
- Antiarrythmic and antianginal action.
- An added bonus for the elderly patients is improvement of senile tremor (Massie, 2001: 458).

➢ **ACE inhibitors**

ACE inhibitors are being increasingly used as the initial medication in mild to moderate hypertension. They appear to be more effective in younger whites. They are relatively less effective in blacks and in the elderly and in predominantly systolic hypertension (Massie, 2001: 458). They have been demonstrated to be safe and effective in lowering blood pressure and are well tolerated by most patients and do not have any metabolic side effects (WHO, 1996: 56).

A number of ACE inhibitors have been identified and approved for the treatment of hypertension by the food and drug administration (FDA) vs. (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril and trandolapril).

Their primary mode of action is inhibition of the renin-angotensin-aldosterone system, but they also inhibit bradykinin degradation, stimulate vasodilating prostaglandins synthesis, and sometimes, reduce sympathetic nervous system activity. These later actions may explain why they exhibit some effect even in patients with low plasma renin activity (Massie, 2001: 458).

ACE inhibitors have not yet been shown to decrease cardiovascular morbidity and mortality in hypertensive patients. However, they have been shown to control morbidity and mortality in patients with congestive heart failure and after myocardial infarction in patients with reduced ejection fraction by mitigating left ventricular dilation. They have also been shown to be very effective in reducing the development of left ventricular hypertrophy in hypertensive patients and retarding the progression of renal disease in patients with insulin-dependant diabetes mellitus and moderate renal impairment (WHO, 1996: 56).

ACE inhibitors are becoming increasingly popular in younger patients as drugs of first choice but are probably less effective as monotherapy in the elderly (although in combination with a small dose of a diuretic they are usually very well tolerated and help offset some of the diuretic's side effects). For the selected patients whose blood pressure responds well to one of these agents alone, it is probably one of the best tolerated modes of treatment because of the lack of annoying side effects such as drowsiness or impotence, and because adverse reactions of ACE inhibition are usually predictable and if not apparent at the fist few days or weeks, unlikely to occur at a later stage (Rosenthal & Silverberg, 1987: 65).

ACE inhibitors are the agents of choice in type I diabetics with frank proteinuria or evidence of renal dysfunction, because they delay the progression to end-stage renal failure. They are also the drugs of choice (usually in conjunction with a diuretic) in patients with congestive heart failure and are indicated also in asymptomatic patients with reduced ejection fraction, whether post myocardial infarction or from other causes (Massie, 2001: 462).

THE ADVANTAGES:

- Relative freedom from troublesome side effects.
- They delay the progression of other forms of renal disease.
- They reduce the number of cardiovascular deaths, nonfatal myocardial infarctions and nonfatal strokes, and instances of new-onset heart failure in population of patients at high risk for vascular events (Massie, 2001: 461-462).

THE CONTRAINDICATIONS:

- Patients with bilateral stenosis of the renal arteries.
- Pregnancy (they are strongly contraindicated in the second half of pregnancy since they may cause fetal and neonatal death).
- Prescribed in low doses to patients with impaired renal function (WHO, 1987: 64).

THE SIDE EFFECTS:

- Chronic dry cough due to bronchial and laryngeal irritation.
- Dizziness.
- Skin rashes.
- Taste alterations are seen more often with captopril.
- Angioedema due to their second inhibition of kininase (Massie, 2001: 458).

➢ **Calcium channel blocking agents**

More recently, calcium channel blockers have become increasingly popular in the treatment of hypertension in the elderly. As antihypertensive agents they are widely prescribed, especially for patients with coexisting coronary disease or with contraindications to the use of thiazides (Rosenthal & Silverberg. 1987: 63).

There are three major groups of calcium antagonists with distinctly different properties: the phenylalkylamines, dihydropyridines and benzothiazepines (WHO, 1996: 56). All the agents of

these classes reduce blood pressure and a number of new agents with a longer duration of action and perhaps less negative inotropic activity are available (Massie, 2001: 462).

The calcium channel blockers act by causing peripheral vasodilatation, which is associated with less reflex tachycardia and fluid retention than other vasodilators. These agents are effective as single drug therapy in approximately 60% of patients and appear to be effective in all demographic groups and all grades of hypertension. As a result they may be preferable to beta-blockers or ACE inhibitors (Massie, 2001: 462).

SIDE EFFECTS:

- Headache and flushing
- Peripheral oedema
- Bradycardia
- Constipation
- Heart failure in patients with cardiac dysfunction due to their negative inotropic effect

(Massie, 2001: 462)

➢ **Alpha-adrenergic blockers**

Alpha-adrenergic blockers are safe and effective in lowering blood pressure (WHO, 1996: 6). They block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance. These agents are effective as single drug therapy in some individuals but tachycardia may appear during long-term therapy (Massie, 2001: 462).

Alpha-adrenergic blockers have little place in the treatment of chronic hypertension in the older patients, except for the rare case of an inoperable pheochromocytoma (Rosenthal & Silverberg, 1987: 65).

There is some evidence that alpha-blockers may have advantages in patients with hyperlipidaemia or glucose intolerance. As with the other newer agents, there are no long-term clinical trials demonstrating reduction in morbility or mortality in hypertensive patients treated with alpha-blockers (WHO, 1996: 56).

SIDE EFFECTS:

- Marked hypotension and syncope.
- Postdosing palpitations.
- Headache and nervousness may continue to occur during chronic therapy (Massie, 2001: 465-466).

➢ **Combination of drugs**

WHO (1996: 57) asserts: if a drug from any of the five major pharmacological classes is ineffective in lowering blood pressure in a given patient, it is reasonable to substitute a drug from a different class. If therapy with a single drug is only partly effective, it may be preferable to add a small dose of a second drug from another class rather than increase the dose. This permits the addition of different primary actions while minimising the homeostatic compensation that limits the fall in pressure. Combination therapy also minimises side effects by encouraging the use of drugs in low doses.

An additive effect has been shown when combining:

- A diuretic with a beta-blocker, ACE inhibitor or alpha blocker.
- A beta-blocker with an alpha blocker or a dihydropyridine calcium channel antagonist.
- An ACE inhibitor with a calcium antagonist.

In order to maximise the benefits of treatment in all hypertensive patients, combinations of two and sometimes three drugs may be required. For reasons of convenience, cost and increased patient compliance, preparations that combine two drugs in a single tablet or capsule may be appropriate for many patients once the need and dose for constituent drugs have been established (WHO, 1996: 57).

2.3.7. Guidelines for selecting the first-line drugs for hypertension

Although most prescribers prefer one drug to the other for the treatment of hypertension, it is necessary to have guidelines that will help you decide on which treatment is best for a specific patient (refer to table 2.3).

TABLE 2.3.

Guidelines for selecting first-line drugs for hypertension (WHO, 1996: 54)

CLASS OF DRUG	CONDITION INDICATIONS	CONTRA INDICATIONS	CAUTION / LIMITED VALUE
Diuretics	Heart failure Elderly patients Systolic hypertension Black patients	Gout	Diabetes Hyperlipidaemia Pregnancy[a] Sexually active males
Beta-blockers	Angina After myocardial infarction Tachyarrythmias Pregnancy	Asthma and chronic Obstructive pulmonary disease Peripheral vascular disease Heart block[b]	Hypertriglyceridaemia Insulin-dependant diabetes mellitus Heart failure Athletes and physically active patients Black patients
ACE inhibitors	Heart failure Left ventricular hypertrophy After myocardial infarction Diabetes with microalbuminuria	Pregnancy Bilateral renal artery stenosis	Black patients
Calcium antagonist	Angina Peripheral vascular disease Elderly patients Systolic hypertension Glucose intolerant Black patients	Pregnancy	Congestive heart failure[c] Atrioventricular heart block[d]
Alpha-blockers	Prostatic hypertrophy Glucose intolerance		Orthostatic hypotension

[a] because of reduced plasma volume.

[b] grade II and III atrioventricular block.

[c] verapamil should be avoided or used only with great caution.

[d] verapamil and diltiazem should be avoided or used only with great caution.

2.4. CONGESTIVE HEART FAILURE

2.4.1. Definition of congestive heart failure

Circulatory failure has been classified into acute and chronic forms. The acute form is the circulatory failure that includes shock, syncope and sudden death whereas the chronic form of circulatory failure is known as congestive heart failure (Friedberg, 1962; 124). Congestive heart failure may be defined as an inability of the heart to pump adequate blood into the arterial system, resulting in engorgement in the greater or lesser venous circuits. In general, chronic congestive heart failure is the result of severe primary depression of myocardial contractility or extreme ventricular hemodynamic overloading combined with a secondary diminution of the contractile state (Mason, 1976: 293).

It occurs when the cardiac output is inadequate to provide the oxygen needed by the body. Although it is believed that the primary defect in early heart failure resides in the excitation-contraction coupling machinery of the heart, the clinical condition also involves many other processes and organs, including the baroreceptor reflex, the sympathetic nervous system, the kidneys, the renin-angiotensin-aldosterone system, vasopressin, and death of cardiac cells (Katzung & Parmeley, 1998: 199).

Congestive heart failure is a syndrome with multiple causes that may involve the right ventricle, the left ventricle, or both. Cardiac output in congestive heart failure is usually below the normal range. This ventricular dysfunction may be primarily systolic (i.e. inadequate force generation to eject blood normally) or diastolic (i.e. inadequate relaxation to permit normal filling). Systolic dysfunction, with reduced cardiac output and significantly reduced ejection fraction (less than 45%), is typical of acute failure, especially that resulting from myocardial infarction (Katzung & Parmeley, 1998: 199).

The primary signs and symptoms of all types of congestive heart failure include tachycardia, decreased exercise tolerance and shortness of breath, peripheral and pulmonary edema, and cardiomegaly. Decreased exercise tolerance with rapid muscular fatigue is the major direct consequence of diminished cardiac output. The other manifestation results from the attempts of the body to compensate for the intrinsic cardiac defect (Katzung & Parmeley, 1998: 199).

2.4.2. Classification of congestive heart failure

As Friedberg (1962: 157) has stipulated, classification of patients with congestive heart failure has proved useful in evaluating their functional status and in prognosis. Different classes have come up in the literature study:

Class 1. Patients with cardiac disease but with no limitation of physical activity. Ordinary physical activity causes no undue dyspnea, anginal pain, fatigue, or palpitation.

Class 2. Patients with slight limitation of physical activity. They are comfortable at rest and with mild exertion. They experience symptoms only with the more strenuous grades of ordinary activity.

Class 3. Patients with marked limitation of physical activity. They are comfortable at rest, but experience symptoms even with the milder forms of ordinary activity.

Class 4. Patients with inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present, even at rest, and intensified by activity.

2.4.3. Etiology of congestive heart failure

The course and cause of death in congestive heart failure are often determined or modified by the underlying cardiac disease. Death is often precipitated by a pulmonary or cerebral embolism and infarction or by an acute coronary occlusion (Friedberg, 1962: 57).

The precipitating causes include the clinical conditions which, because of their close sequential relationship, appear to be concerned in the onset of the symptoms of heart failure. The underlying causes of heart failure comprise those diseases which injure the pericardium, myocardium, valves or peripheral vessels and thereby bring about functional and anatomic changes in the heart or vascular system which eventually lead to cardiac failure (Friedberg, 1966: 215-216).

2.4.4. Prevention of congestive heart failure

It is important to recognize the precipitating causes of heart failure for we can more readily avoid or eliminate these causes than we can other factors in the development of heart failure. For the present, the avoidance of these precipitating factors offers the most direct and the most promising approach to the prevention of heart failure (Friedberg, 1962: 139).

2.4.5. Management of congestive heart failure

The aim of treatment in congestive heart failure will be to improve cardiac function as much as possible and to reduce the activities of the patient to bounds within the capacity of his heart. It will seldom be possible to restore anatomical integrity of the heart and it will be equally difficult in most instances to eradicate the underlying causative disease responsible for functional or structural changes in the heart (WHO, 1996: 67).

2.4.5.1. General measures

The major steps in the management of patients with chronic heart failure according to WHO (1996b: 67) are:

- Reduce workload of the heart

Reduction of cardiac work is a traditional form of therapy that is extremely helpful in most cases. It can be accomplished by reducing activity levels, weight reduction is especially important in the control of hypertension.

- Restrict sodium

Sodium restriction is an important measure. Despite the availability of efficacious diuretics, one should advise the patients about the necessity for salt restriction and encourage them to avoid excess salt through dietary restraint.

- Restrict water

Restricting the amount of water intake may be necessary though rarely required.

- Bed rest

It is almost a platitude to say that bed rest is essential in the treatment of heart failure. Rest slows the heart rate and reduces the cardiac output to a fraction of what it would be even at moderate activity.

- Diet

The proper functioning of the heart is improved appreciably by the intake of selected foodstuff. An appropriate diet can make a considerable difference to the heart's performance and should be planned carefully. Hence the diet should be so regulated that nutritional requirements are met, but with minimum demands on the heart (WHO, 1996: 67).

2.4.5.2. Surgical treatment

The presence of congestive heart failure or a history of its occurrence in the past constitute a serious risk and no operation should be performed on such patients unless urgently necessary to save life. Notable exceptions are surgical obliteration of the patent ductus arteriosus, excision of coarctation of the aorta, decortication of constrictive pericarditis, and the removal of the burden of thyrotoxicosis and similar conditions (WHO, 1996: 68).

2.4.5.3. Drug treatment

- Treatment of congestive heart failure:

Congestive heart failure is usually responsive to positive inotropic drugs, at least initially. Diastolic dysfunction often occurs as a result of hypertrophy and stiffening of the myocardium,

and although cardiac output is reduced, ejection fraction may be normal. Congestive heart failure due to diastolic dysfunction does not usually respond optimally to positive inotropic drugs (Kutzung & Parmeley, 1998: 199).

Drugs with positive inotropic effect:

I. Digitalis

Digitalis has been a valuable agent in the treatment of congestive heart failure since 1785 (Friedberg, 1962: 139). It has two different effects on the heart, namely, the mechanical and electrical functions. The therapeutic action of digitalis on mechanical function is to increase the intensity of the interaction of the actin and myosin filaments of the cardiac sarcomere. As such the net result of the action of therapeutic concentrations of a cardiac glycoside is a distinctive increase in cardiac contractility. The effects of digitalis on the electrical properties of the heart are a mixture of direct (an early brief prolongation of the action potential, followed by a protracted period of shortening thus leading to the shortening of atrial and ventricular refractoriness) and autonomic actions (involves both the parasympathetic and the sympathetic systems by sensitisation of the baroreceptors, central vagal stimulation, and facilitation of muscuranic transmission at the cardiac muscle cell) (Katzung & Parmeley, 1998: 203;204).

Thus the major therapeutic effects are those exerted on the heart, the most important being slowing of the heart rate and increasing in the strength of myocardial contraction (WHO,1996: 68).

II. Bipyridines

The bipyridines increase myocardial contractility without inhibiting Na+/k+ ATPase or activating adrenoceptors. They appear to increase inward calcium flux in the heart during the action potential and alter the intracellular movements of calcium by influencing the sarcoplasmic reticulum. They also have a significant vasodilating effect that undoubtedly contribute to their therapeutic benefit in heart failure (Katzung & Parmeley, 1998: 204;205).

Drugs without positive inotropic effect:

I. Diuretics

The mechanism of action of diuretics in congestive heart failure is to reduce salt and water retention, thereby reducing ventricular useful effects i.e. reduction of edema and its symptoms and reduction of cardiac size, which leads to improved efficiency of pump function (Katzung & Parmeley, 1998: 206).

II. Angiotensin-converting enzyme inhibitors

The angiotensin-converting enzyme inhibitors are used in congestive heart failure since they reduce peripheral resistance and thereby reduce afterload; they also reduce salt and water retention (by reducing aldosterone secretion) and in that way reduce preload. The reduction in tissue angiotensin levels also reduces sympathetic activity, probably through diminution of angiotensin's presynaptic effects on norepineprine release. Finally these drugs reduce the long term remodelling of the heart and vessels, an effect that may be responsible for the observed reduction in mortality and morbidity (Katzung & Parmeley, 1998: 206,207).

III. Vasodilators

The vasodilators are effective in congestive heart failure because they provide a reduction in preload (through venodilation), or reduction in afterload (through arteriolar dilation), or both. Some evidence suggests that long-term use of hydralazine and isosorbide dinitrate can also reduce damaging remodelling of the heart (Katzung & Parmeley, 1998: 207).

2.5. GENERAL EMPHASIS ON THE TREATMENT OF HEART DISEASES

When treating patients of the older age group, one should be more cautious with the side effects of drugs or the coexistence of other diseases, since these patients are more likely to be under treatment for several conditions. One should be more aware of what other medications the patient is receiving so that adverse drug interaction may be avoided, or drugs may be chosen which benefit one condition without adversely affecting the other. It should also be kept in mind that elderly patients frequently require smaller doses than those used in younger adults. Otherwise, the same general considerations regarding drug side effects and interactions apply to this as any other age group (Rosenthal & Silverberg, 1987: 66).

2.6. SUMMARY OF THE CHAPTER

ACE inhibitors have become an important therapeutic modality in the management of patients with congestive heart failure and hypertension. Because of the successes of the initial agents, many more have become available. Despite much clinical experience, direct comparison between ACE inhibitors are few, with generally no significant advantage of one agent over another in terms of efficacy, adverse effect, profile or effects on quality of life (Rosenthal & Silverberg, 1987: 66).

The majority of ACE inhibitors now available are prodrugs, most of which are converted to active diacids that are then renally excreted. Besides the prodrug, the other major drug groups are captopril-like or drugs that are not metabolised, such as lisinopril. Although these are totally different kinds in terms of their pharmacology, they are the same in efficacy as Rosenthal and Silverberg (1987: 66) have stipulated.

CHAPTER 3

PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS

3.1 INTRODUCTION

In this chapter, pharmacoepidemiology and pharmacoeconomics will be discussed as principles of cost analysis.

3.2 COST ANALYSIS

According to Beyea and Nicoll (quoted by Viljoen 2002:76), the term "cost analysis" is used widely and is therefore sometimes abused. Cost analysis in health care is defined as a process that examines costs related to a specific clinical process or event. The reason for a cost analysis to be performed is to provide information that will help decision-makers to determine how resources will be allocated. Expenses may include direct and indirect costs. Outcomes and benefits may be reflected by clinical measures or financial calculations based on the projected benefit or outcome.

The price of a drug product is not the same as the cost of drug therapy. The objective of this chapter is to clarify these differences by defining and prescribing the concept of cost according to pharmacoepidemiologic and pharmacoeconomic approaches. The concept of cost deals with the resources that are used or consumed in the production of goods or a service (Larson, 1996:45). This concept leads us to the understanding that there is a difference between cost of illness and cost of therapy.

Cost of illness (according to Larson, 1996: 47):

An illness consumes resources and, thus, it has a cost. The cost of an illness is the sum of four components:

- The medical resources used to treat the illness.
- The non-medical resources associated with it.
- Loss of productivity due to illness or disability (indirect cost).
- The intangible cost of pain and suffering, which is often unquantifiable.

(All of these will be discussed in more detail under costs in pharmacoeconomics).

3.3 PHARMACOEPIDEMIOLOGY

3.3.1 Definition of pharmacoepidemiology

Pharmacoepidemiology is a relatively new field of study, with concepts, methods and applications that have made increasing contributions to health care as the field has evolved over the past few decades (Einarson *et al.*,1997:372). It is the study of the use and effects of drugs in large numbers of people (Strom, 1994:3). Pharmacoepidemiology can also be defined as the application of epidemiological reasoning, methods and knowledge to the study of the uses and effects (beneficial and adverse effects) of drugs in human populations. It therefore aims to describe, explain, control and predict the uses and effects of pharmacological treatment in a defined time, space and population. Pharmacoepidemiology also examines the relationship between drug exposure and health outcomes in defined populations (Lamprecht & Schutte, 2002:175).

The term pharmacoepidemiology contains two components: *pharmaco* and *epidemiology* (Lamprecht & Schutte, 2002:175). It summarises two different areas: pharmacology (the study of interactions between drugs and living organisms) and epidemiology (the study of the relationship between diseases and biological phenomena and other factors (e.g. lifestyle, environment, social setting and individual traits) that could influence the frequency distribution and evolution of these diseases). As such, pharmacoepidemiology could be defined as the study of interactions between drugs and populations (Begaud, 2002: 1). The core of pharmacoepidemiology lies at the intersection of clinical pharmacology and clinical epidemiology (Lamprecht & Schutte, 2002:175).

Pharmacological studies range in focus from very specific to very broad. These studies may examine a single individual (for example, a case report of a rare drug reaction), or large groups

of people followed for many years. Table 3.1 identifies the focus of pharmacoepidemiology and the related fields of drug utilisation and clinical pharmacology. In general, clinical pharmacology is concerned with drug effects in individual patients. Drug utilisation focusses on drug usage patterns and appropriateness of drug use in groups. Pharmacoepidemiology examines the relationship between drug exposure and health outcomes in defined populations (Truter, 1999:54,55).

TABLE 3.1

Focus of pharmacoepidemiology and related areas of study (Einarson *et al.*,1997:375).

DISCIPLINE	**FOCUS**	**INDICATOR OF DRUG EXPOSURE**	**RESULT STUDIED**
Clinical pharmacology	Individual patient	Clinical effect	Drug effectiveness
		Adverse reaction	Drug toxicity
Drug utilisation	groups	Utilisation patterns	Excessive or inadequate use
		Appropriateness of use	Quality of care
		Correlation with outcome	Drug safety, possible relationships
Pharmacoepidemiology	Populations (defined)	Exposure-outcome relationship	causality
		Comparative effectiveness	Quantification of benefit
		Comparative toxicity	Quantification of risk

Pharmacoepidemiology applies the method of epidemiology to the content area of clinical pharmacology. Therefore, in order to understand the approaches and methodological issues specific to the field of pharmacoepidemiology, the basic principles of the field of clinical pharmacology and epidemiology must be understood.

- **Clinical pharmacology**

Clinical pharmacology is the study of the effects of drugs in humans. It is traditionally divided into two basic areas, namely pharmacokinetics and pharmacodynamics. Pharmacokinetics is the study of the relationship between the dose administration of a drug and the serum or blood level achieved. It deals with drug absorption, distribution, metabolism and excretion. Pharmacodynamics is the study of the relationship between drug level and drug effect. Together these two fields allow one to predict the effect one might observe in a patient from administering a certain drug regimen. Pharmacoepidemiology encompasses elements of both these fields, exploring the effects achieved by administering a drug regimen but it does not normally involve or require the measurement of drug level (Strom, 1994:4).

During recent years, the field of pharmacology has increased dramatically from molecules and cells to include humans. It is now necessary to investigate drugs not only on human beings (i.e. clinical pharmacology) but also to further evaluate the effect of drugs on large populations under real life conditions. Pharmacoepidemiolgy, which can be considered as a populational pharmacology, aims to complete the evaluation of drugs made before approval. Pharmacoepidemiological studies facilitate the investigation of the characteristics of treated populations of patients, drug associations in real clinical practice, the most commonly used dosages, infrequent adverse drug reactions and unexpected long-term benefits (Begaud, 2002: 1).

- **Epidemiology**

Epidemiology is the study of disease occurrence and transmission in a human population. Epidemiological studies focus on the distribution and determinants of diseases in populations. Epidemiology may also be considered as the method of public health - a scientific approach to studying disease and health problems (Waning & Montagne, 2001:1-2). It began as the study of infectious diseases in large populations, that is epidemics. More recently it has been concerned with the study of chronic diseases as well (Strom, 1994:5).

Epidemiology consists of research methods and specific strategies for counting and calculating the occurrence and risk of disease. Therefore, epidemiological studies of drug use employ these methods and statistical measures to study the occurrence and distribution of drug use and its

associated problems (Waning & Montagne, 2001:2). It is an eclectic discipline comprising facets of sociology, staffs, medicine and demography. Although its development may be traced back to the industrial revolution of the 1600s, it was not until the 19th century that it was recognised as a subject area in its own right (Batty, 1999: 1).

- **Pharmacoecoepidemiology**

The basic idea of pharmacoepidemiology is to measure the source, diffusion, use and effects of drugs in a population and to determine the frequency and distribution of drug use outcomes in that population. From this information, the nature and extent of specific types of drug use can be determined, and both potential and realised problems can be solved (Waning & Montagne, 2001:5).

Pharmacoecoepidemiology uses techniques of chronic disease epidemiology to study the use and the effects of drugs. It draws on the knowledge and techniques of a number of related disciplines, particularly epidemiology, biostatistics, pharmacology, clinical medicines, psychology, sociology and economics. The studies range in focus from very specific to very broad (Lamprecht & Schutte, 2002:176).

Pharmacoepidemiology develops three kinds of study:

- Studies of drug effectiveness on large populations monitored during long-term periods.
- Studies of adverse drug reactions with quantification of risk
- Drug utilisation studies to assess the characteristics of drug prescription or consumption according to evidence-based data or official guidelines. These latter studies also investigate differences in drug prescriptions according to national or regional habits, characteristics of the patient (e.g. age, gender and race) and physicians, among other things (Begaud, 2002: 1).

The field of pharmacoepidemiology has primarily concerned itself with the study of adverse effects. Adverse reactions have traditionally been separated into those that are the result of an exaggerated but otherwise usual pharmacological effect of the drug, the so-called *type A reactions* (which are common, dose-related, predictable, and less serious and which can usually

be treated by simply reducing the dose of the drug), vs. those that have aberrant effects, the so-called *type B reactions* (which are uncommon, not related to dose, unpredictable, and potentially more serious and which usually require cessation of the drug and may be due to what are known as hypersensitivity reactions or immune reactions). Type B reactions are the most difficult to predict or even detect, and represent the major focus of pharmacoepidemiologic studies of adverse drug reactions (Strom, 1994:4).

Currently, pharmacoepidemiology focusses on pharmaceutical care outcomes and the identification of potential or realised drug use problems. The discipline's basis in epidemiology provides a theoretical foundation for examining the sources of supply and flow of drugs throughout a population as well as the effects experienced by individual drug users in that population. This area of research has also been used to study illicit, or non-medical, drug use - a means to determine outbreaks of increased use, called drug epidemics (Waning & Montagne, 2001:4).

3.3.2 Reasons to perform pharmacoepidemiological studies

The decision to conduct a pharmacoepidemiological study could be viewed as similar to the regulatory decision about whether to approve a drug for marketing or the clinical decision about whether to prescribe a drug. In each case decision making involves weighing the cost and the risks of a therapy against its benefits.

The main costs of a pharmacoepidemiological study are obviously the cost of conducting the study itself. These will clearly vary, depending on the questions posed and the approach chosen to answer them. With the exception of post-marketing randomised clinical trials, the cost per patient is likely to be less than the cost of a pre-marketing study. Other costs to consider are the opportunity costs of other research, which might be left undone if this research were performed (Strom, 1994:57).

The future of pharmacoepidemiological studies has unlimited potential. This field represents the primary scientific approach for the pharmaceutical profession's new mission in patient care. Its approaches and techniques for assessing the nature and extent of drug use and the reasons

behind unsafe or irrational use will allow the development of strategies to prevent or limit drug use problems (refer to table 3.2).

TABLE 3.2

The purpose of pharmacoepidemiological studies

(Strom, 1994:58)

A. Regulatory
   1. Required
   2. To obtain earlier approval for marketing
   3. As a response to question by regulatory agency
   4. To assist application for approval for marketing elsewhere

B. Marketing
   1. To assist market penetration by documenting the safety of the drug
   2. To increase name recognition
   3. To assist in repositioning the drug
      a. Different outcomes, e.g. quality-of-life and economic evaluation
      b. Different types of patients, e.g. the elderly
      c. New indications
      d. Less restrictive labelling

C. Legal
   1. In anticipation of future product liability litigation

D. Clinical
   1. Hypothesis testing
      a. Problem hypothesised on the basis of drug structure
      b. Problem suspected on the basis of pre-clinical or pre-marketing human data
      c. Problem suspected on the basis of spontaneous reports
      d. Need to better quantify the frequency of adverse reactions
   2. Hypothesis generating - Need depends on whether:
      a. It is a new chemical entity
      b. The safety profile of the drug class
      c. The relative safety of the drug within its class
      d. The formulation
      e. The disease to be treated, including

i. its duration;

ii. its prevalence;

iii. its severity; and

iv. whether alternative therapies are available.

3.3.2.1 Regulatory

- The clearest and most compelling reason to perform a post-marketing pharmacoepidemiological study is regulatory, when a plan for a post-marketing pharmacoepidemiological study is required before the drug is approved for marketing. Requirements for post-marketing research have become progressively more frequent in recent years. In fact, since the early 1970s the FDA has required post-marketing research at the time of approval for about one third of all newly approved drugs.
- Sometimes a manufacturer may offer to perform a pharmacoepidemiological study with the hope that the regulatory agency might thereby approve the drug's earlier marketing. If the agency believed that a serious problem would be detected reliably and rapidly after marketing, it could feel comfortable releasing the drug sooner.
- Some post-marketing studies of drugs arise in response to case reports of adverse reactions reported to the regulatory agency. One response to such a report might be to suggest a labelling change. Often a more appropriate response clinically and commercially would be to propose a pharmacoepidemiological study.
- Finally, drugs are obviously marketed at different times in different countries. A post-marketing pharmacoepidemiological study conducted in a country which marketed a drug relatively early could be useful in demonstrating the safety of the drug to regulatory agencies in countries that have not yet permitted the marketing of the drug (Strom, 1994:58, 59).

3.3.2.2 Marketing

- Because of the known limitations in the information available about the effects of a drug at the time of its initial marketing, many physicians are proprietary hesitant to prescribe a drug until a substantial amount of evidence in its use has been gathered. A formal post-marketing

surveillance study can speed that process, as well as clarify any advantages or disadvantages a drug has to its competitors.

- A pharmacoepidemiological study could also be useful to improve product name recognition. The fact that a study is underway will often be known to prescribers, as will its results once it is publicly presented and published. This increased name recognition will presumably help sales. An increase in a product's name recognition is particularly likely to result from pharmacoepidemiological studies that recruit subjects for the study via prescribers.
- A pharmacoepidemiological study could also be useful to reposition a drug that is already on the market - that is, to develop new markets for the drug. One could explore different types of outcomes resulting from the use of the drug for the approved indication, e.g. the impact of the drug on the cost of medical care and on the patient's quality of life. One could also explore the use of the drug for the approved indication in types of patients other than those included in pre-marketing studies, e.g. in children or the elderly. By exploring unintended beneficial effects, or even drug efficacy, one could obtain clues to and supporting information for new indications for drug use. Whether because of questions about efficacy or questions about toxicity, drugs are sometimes approved for initial marketing with restrictive labelling.
- Finally, and perhaps most importantly, pharmacoepidemiological studies could be useful to protect the major investment made in developing and testing a new drug. When a question arises about a drug's toxicity, it often needs an immediate answer, or else the drug may lose market-share or even be removed from the market.

  (Strom, 1994:59, 60).

3.3.2.3 Legal

Post-marketing surveillance studies could theoretically be useful as legal prophylaxis, in anticipation of eventually having to defend against product liability suits. All drugs cause adverse effects. The regulatory decision to approve a drug and the clinical decision to prescribe a drug both depend on a judgement about the relative balance between the benefits of a drug and its risks. Therefore, pharmacoepidemiological studies could make easier the defence of totally groundless suits in which a drug is blamed for producing adverse reactions it does not cause (Strom, 1994:60).

3.3.2.4 Clinical

- The major reason for most pharmacoepidemiological studies is hypothesis testing. The hypothesis to be tested could be based on the structure of the chemical class of the drug. Alternatively, hypotheses could also be based on pre-marketing or post-marketing animal or clinical findings, e.g. hypotheses could come from spontaneous reports of adverse events experienced by patients taking the drug in question. Finally, an adverse effect may clearly be due to a drug, but a study may be needed to quantify its frequency (Strom, 1994:60).

- Hypothesis-generating studies are intended to screen for previously unknown and unsuspected drug effects.
  - The safety profile of the class of drugs should also be important in the decision about whether to conduct a formal screening post-marketing surveillance study.
  - The relative safety of the drug within its class could be helpful. The drug that has been studied in large numbers of patients prior to marketing and which appears safe is less likely to need supplementary post-marketing surveillance studies.
  - The formulation of the drug could be considered a determinant of the need for formal screening pharmacoepidemiological studies. A drug that will be used mainly in institutions where there is close supervision, may be less likely to need such a study. Any serious adverse effect is likely to be detected, even without any formal study.
  - The disease to be treated is an important determinant of whether a drug needs additional post-marketing surveillance studies. It is also important to know whether the alternative therapies are available.

    (Strom, 1994:60, 61).

TABLE 3.3

Problem-solving with pharmacoepidemiology

(Waning & Montagne, 2001:7)

Medical drug use
Beneficial effects of drug therapy
Risks (e.g. adverse reactions, side-effects) of drug therapy
Inappropriate prescribing behaviours
Patient non-compliance
Irrational self-medication practices
Poor drug use outcomes
Cost-effectiveness of drug therapy
Non-medical drug use
Social-recreational drug use and associated problems
Acute incidents of drug toxicities
Chemical dependencies
Outbreaks and sources of drug epidemics

With these pharmacoepidemiologic tools and methods, the products of drug development can be used more effectively, while minimising problems, for the benefit of both individual patients and society (refer to table 3.3) (Waning & Montagne, 2001:7).

As in all the other studies, there are risks and benefits to conducting a pharmacoepidemiological study.

1. RISKS

- The possibility that it could identify an adverse outcome as associated with the drug under investigation when in fact the drug does not cause this adverse outcome.
- It could provide false reassurance about a drug's safety.

Both these risks can be minimised by appropriate study designs, skilled researchers, and appropriate and responsible interpretation of the results obtained (Strom, 1994:57).

2. BENEFITS

The benefits of pharmacoepidemiological studies could be conceptualised in four different categories according to Waning and Montagne (2001:7): regulatory, marketing, clinical and legal (see table 3.3). Each will be of importance to different organisations and individuals involved in deciding whether to initiate a study. Any given study will usually be performed for combination of these reasons.

3.3.3 Methods used in pharmacoepidemiology

Pharmacoepidemiology as mentioned previously, applies the methods of epidemiology used to the context area of clinical pharmacology. The methods used in pharmacoepidemiology involve both analytical (i.e. quantitative) and descriptive (i.e. qualitative) approaches. Descriptive approaches are generally aimed at evaluating how drugs are being prescribed and used, and may be used as part of a quality assurance programme. They can thus be directly linked to a disease management and an evidence-based medicine approach, where the focus is on quality assurance and quality improvement.

Two types of drug effects are of interest in pharmacoepidemiology, namely safety and effectiveness. The ideal model for the evaluation of effectiveness is the double blind randomised controlled trial. However, for methodological, practical and economic reasons, this method is rarely applied in post-marketing drug surveillance. A number of non-experimental methods are therefore usually applied to marketed drugs. All the methods that are used in pharmacoepidemiology are useful in some way, but each model has its unique applications, advantages and disadvantages. The most important pharmacoepidemiological models are listed in table 3.3 and are briefly discussed here under (Truter, 1999:56).

TABLE 3.4

Overview of pharmacoepidemiological methods

Adapted from Edlavitch (quoted by Truter, 1999:57)

DESCRIPTIVE OBSERVATIONAL STUDIES
Individual-based
Case reports
Case series
Population-based (correlation studies)
Secular trend analyses (ecological studies)
Cross-sectional studies
Drug utilisation studies
ANALYTICAL STUDIES
Observational studies
Cohort studies
Case-control studies
Case crossover designs
Case-cohort studies
Intervention studies (trials)
Controlled clinical trials
Randomised, controlled clinical trials (blinded or unblinded)
Other experimental approaches

3.3.4 Descriptive observational studies

Observational studies are those in which the investigator has no control over who receives what kind of drugs. The following five types of observational studies are briefly discussed below: case reports, case series, secular trend analyses, cross-sectional studies and drug utilisation studies.

3.3.4.1 Case reports

Case reports are simply reports of single patients. As used in pharmacoepidemiology, a case report describes a single patient that was exposed to a drug and experienced a particular - usually adverse - outcome. Case reports are useful for raising hypotheses about drug effects, to be tested with more rigorous study designs. However, in a case report one cannot determine whether the patient reported is either typical of those with the exposure or typical of those with the disease. Certainly, one can usually not determine whether the adverse outcome was due to drug exposure or would have happened anyway. As such, it is very rare that a case report can be used to make a statement about causation. One exception to this would be when the outcome is so rare and so characteristic of the exposure that one knows that it was likely to be due to the exposure, even if the history of the exposure were unclear.

Another exception would be when the disease course is very predictable and the treatment causes a clearly apparent change in this disease course. Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, and can be treated again when the change occurs upon treatment (Strom, 1994:20, 21).

3.3.4.2 Case series

Case series are collections of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described. They are often from a single hospital or medical practice. Alternatively, case series can be collections of patients with a single outcome, whose antecedent exposures are then examined.

After drug marketing, case series are most useful for two related purposes.

- Firstly, they can be useful for quantifying the incidence of an adverse reaction.
- Secondly, they can be useful for ensuring that any particular adverse effects of concern do not occur in a population that is larger than that studied prior to drug marketing.

In this type of study, one can be more certain that the patients are probably typical of those with the exposure or with the disease, depending on the focus of the study. However, in the absence

of a control group, one cannot be certain which features in the description of the patients are unique to the exposure, or outcome (Strom, 1994:21).

A single case report may therefore indicate an individual reaction and /or an extremely rare phenomenon. The case series provides evidence that a finding - even though still rare - is repeated. The major advantage of a case series is that it is often an early warning system.

3.3.4.3 Analyses of secular trend

Analyses of secular trends, also called ecological studies, examine trends in an exposure considered as a presumed cause and trends in a disease considered as a presumed effect, and test whether the trends coincide. These trends can be examined over time or across geographic boundaries. In other words, one could analyse data from a single region and examine how it changes over time, or one could analyse data from a single time period to compare how the data differ from region to region or country to country. Vital statistics are often used for these studies.

Analyses of secular trends are useful for rapidly providing evidence for or against a hypothesis. However, these studies lack data on individuals, because they only study groups. As such, they are unable to control for confounding variables. Thus, among exposures whose trends coincide with that of the disease, analyses of secular trends are unable to differentiate which factor is likely to be the true cause (Strom, 1994:22).

3.3.4.4 Cross-sectional studies

Cross-sectional studies are sometimes called prevalence studies. They are studies of total populations or population groups in which information is collected about the present and past characteristics, behaviours or experiences of individuals. Cross-sectional studies can be of value in predicting the future spread of certain diseases. They are based on a sample of the whole population and do not rely on individuals presenting themselves for medical treatment (Waning & Montagne, 2001:51, 52).

3.3.4.5 Drug utilisation

Drug utilisation can be defined as the study of the prescribing, dispensing, administering and ingesting of drugs. This definition recognises the steps and processes in drug usage and the problems that may arise in each of these steps. The World Health Organisation (WHO) expands on this definition of drug utilisation by including outcome variables (Serradell *et al.*, 1987:994).

According to Wade (quoted by Badenhorst, 2002:98) drug utilisation studies are aimed at detecting inappropriate drug use. The aim of drug utilisation studies is to be able to carry out a complete therapeutic audit, in other words, to analyse what is prescribed, with what intention, and with what benefit or what ill- effects and at what cost to the community.

3.3.5 Analytical studies

The following five types of analytical studies are briefly discussed in this section: cohort studies, case-control studies, case crossover designs, case-cohort studies and interventional studies.

3.3.5.1 Cohort studies

A cohort study design usually consists of a prospective, observational, analytical study. It is an incidence study that is usually prospective or longitudinal and that measures attributes in a population free of the outcome of interest (e.g. disease, drug use) and relates them to subsequent development of the disease or outcome in that population as it is followed over time. This design is as close to an experimental approach as possible while still being observational in nature. It is used to study the risk of disease development (Waning & Montagne, 2001:56).

Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies generally are used to compare exposed patients to unexposed patients, although they can also be used to compare one exposed subset to another (Strom, 1994:22, 23).

Cohort studies are performed when intentional exposure of human beings cannot be justified. They are observational because the investigator does not determine assignment of exposure but rather passively observes as exposures occur (Waning & Montagne, 2001:56).

3.3.5.2 Case-control studies

The case-control design is an analytical, retrospective study comparing people with the disease (cases) to a sample of people without the disease (controls) with respect to exposures or characteristics of interest. This type of study is done to identify factors that could be responsible for the development of a disease or drug use problem.
Case-control studies are designed to assess association between disease occurrence and exposures (e.g. causative agents, risk factors) suspected of causing or preventing the disease. The case-control study is the primary design for determining association between drug use and side-effects or adverse reactions (Waning & Montagne, 2001:52).

Case-control studies can be particularly useful when one wants to study multiple possible causes of exposures as potential risk factors using the same cases and controls. This design is also particularly useful when studying a relatively rare disease, as it guarantees a sufficient number of cases with the disease. Using case-control studies, one can study rare diseases with markedly smaller sample sizes than those needed for cohort studies. Case-control studies generally obtain information on exposures retrospectively, that is, re-creating events that happened in the past (Strom, 1994:22).

In many situations, a case-control study is more efficient than a cohort study because a smaller sample size is required. One key feature of a case-control study, which distinguishes it from a cohort study, is the selection of subjects based on the disease status. Nevertheless, when case-control studies are well done, subsequent well done cohort studies or randomised clinical trials, if any, will generally confirm their results.

3.3.5.3 Case crossover study design

According to Edlavitch (quoted by Truter, 1999:62) a case crossover design is based on the principle that a brief exposure causes a transient change in the risk of a rare acute outcome in a patient. Periods of time in the past when the patient was not exposed could provide control data. Therefore, in some instances when the briefness of exposure, the transient change, and acute outcome criteria are satisfied, the patient can be used as his or her own control.

3.3.5.4 Case-cohort studies

Edlavitch (quoted by Truter, 1999:62) also stated that a case-cohort study is a hybrid design that is similar to a nested case-control study, but the non-cases (controls) are selected randomly from the original cohort. In a nested case-control study, a defined population is followed for a period of time until a number of incident cases of a disease or unintended drug effects are identified. At a specific point in time, all cases and a sample of non-case (control) are compared with regard to prior exposure to a risk factor. The case-cohort study design has been suggested as an economic alternative to a standard cohort design.

3.3.6 Intervention studies

Intervention studies include: controlled clinical trials, randomised controlled clinical trials and other experimental approaches.

3.3.6.1 Controlled clinical trial

According to Edlavitch (quoted by Truter, 1999:63) a controlled clinical trial is a specific type of experimental prospective cohort study that involves assigning participants to various treatment and control cohorts in such a manner that the cohort, independent of the intervention, is at equal risk of developing the study outcome(s). Cohort members may be treated with an active drug, a placebo, or both.

3.3.6.2 Randomised, controlled clinical trial (blinded or unblinded)

According to Edlavitch (quoted by Truter, 1999:63) the best method for determining the true therapeutic benefit of a new unknown treatment is the randomised, controlled clinical trial. This is a trial in which participants are assigned to treatment or control in a random unbiased fashion, based on probability. The main reasons for randomisation are to avoid selection biases that could be introduced by patients or medical care provider preferences, and to ensure that the alternative study cohorts are the same with respect to known and unknown prognostic factors.

3.3.6.3 Other experimental approaches

Other experimental approaches include smaller trials (including clinical trials - the combination of case reports - and simplified clinical trial) and larger clinical trials. These methods will not be discussed further due to their specialised nature.

3.3.7 Application of pharmacoepidemiology

Pharmacoepidemiological studies can be conducted to

- describe drug use;
- generate hypotheses about drug use and health-related outcomes;
- provide evidence to support a hypothesis generated from descriptive studies, theories or other sources;
- test hypothesised relationships; and
- provide economic data on the cost of disease and therapeutic interventions (Truter, 1999:64).

The most important applications of pharmacoepidemiology are listed in table 3.4.

TABLE 3.5

Applications of pharmacoepidemiology

(Einarson, *et al.*, 1997:382).

CATEGORY	STUDY TYPE	APPLICATION
Non-intervention	Drug utilisation review	Appropriateness of prescribing (observational)
		Quality care
	Prescription audit	Identifying heavy users, prescribers
	Prescription event monitoring	Identifying potential adverse drug reactions
		Measuring incidence
	Post-marketing surveillance	Measuring prevalence
	Case-control studies	Measuring prevalence
		Determining association
	Cohort studies	Measuring incidence
		Determining effectiveness
		Establishing causation (controlling variables)
Interventional	Randomised controlled trial	Determining effectiveness
		Establishing causation

3.3.8 Advantages and disadvantages of the different pharmacoepidemiological methods

The advantages and disadvantages of some of the pharmacoepidemiological methods are provided in table 3.6. The studies are organised in a hierarchical fashion, with the study design getting progressively more complex to perform towards the end of the table.

TABLE 3.6

Advantages and disadvantages of the different pharmacoepidemiological methods

(Strom, 1994:20; Waning & Montagne, 2001:51, 52 & 56)

STUDY DESIGN	ADVANTAGES	DISADVANTAGES
Case reports	Inexpensive and easy method for generating hypotheses	Cannot be used for hypothesis testing
Case series	Easy quantifying of incidence	No control group, so cannot be used for hypothesis testing
Analysis of secular trends	Can provide rapid answers	No control or confounding
Cross-sectional study	Involves a single data collection, thus less expensive and more expedient Provides information and data useful for the planning of health services and medical programmes Provides one-time glimpse at the study population Predicts the future spread of certain diseases.	Cannot show cause-effect relationships Results are representative only of the individual who participates in the study Is not effective if the level of disease rate is very small Does not represent seasonal variation of the disease Has limited value in predicting future occurrence of some diseases
Case-control study	Requires fewer subjects Studies several risk factors Can study multiple exposures Can study uncommon diseases Logistically easier and faster Less expensive	Control selection problematic Possibly biased exposure data No direct measure of incidence and prevalence Not representative of the whole population
Cohort study	Can study multiple outcomes Can study uncommon exposures Selection bias likely Unbiased exposure data Incidence data available	Not efficient for the study of rare disease Possibly biased outcome data More expensive If done properly, may take years to complete
Randomised clinical trial (experimental study)	Most convincing design Only design which controls for unknown or unmeasurable confounders	Most expensive Artificial Logistically most difficult Ethical objections

3.3.9 Strengths and weaknesses of the different pharmacoepidemiological methods

The strengths and weaknesses of the different pharmacoepidemiological models are listed in Table 3.7 below.

TABLE 3.7

Strengths and weaknesses of different pharmacoepidemiological models

(Einarson, *et al.*, 1997:382)

MODEL	STRENGTH	WEAKNESS
Case report	Signal generation	No causation
Case series	Confirms relationship	No causation
Cross-sectional study	Identifies correlating factors Estimate of prevalence	Confounding variables
Longitudinal study	Trends over time detected Can measure effect of events (before-after comparison)	Confounding variables
Non-experimental comparison	Suggests causation	Confounding variables
Case-control study	Measures strength of relationship Least costly model Studies multiple exposures	Causation not certain Controls a single variable Recalls bias
Cohort study	Measures incidence Measures strength of the relationship Controls multiple factors Studies multiple outcomes	Costly Time-consuming
Randomised controlled trial	Established causation Controls all factors The only experimental model	Generalisability Costly Focusses on a single factor

3.3.10 Conclusion

Pharmacoepidemiological studies can be conducted to describe drug use as in this study. As stated above, pharmacoepidemiology is an application of epidemiological reasoning, methods and knowledge to the study of the uses and effects of drugs in human populations. According to Porta *et al.* (quoted by Truter, 1999:76) it offers a way of reasoning; a rich set of methods, and a body of substantive knowledge that can both expand the health benefits of drugs and reduce possible risks.

3.4 PHARMACOECONOMICS

In this section, the definition, aim and basic methodologies of pharmacoeconomics will be discussed.

3.4.1 Definition of pharmacoeconomics

Pharmacoeconomics is a relatively new research area that has only become widely used during the past decade. It is an evolving discipline that is dedicated to the study of how different approaches to patient care and treatment influence the resources consumed in healthcare (Truter, 1997:19).

Pharmacoeconomics is the area of health-care research that evaluates and compares the cost and outcomes associated with drug therapy (Waning & Montagne, 2001:143). As stated by Townsend (quoted by Lombard, 2000:55) it has been formally defined as the description and analysis of the cost of drug therapy to healthcare systems and society.

According to Lipsy (quoted by Badenhorst, 2002:83) pharmacoepidemiology is defined as a measure of drug impact on the cost of improving healthcare and it is stated that pharmacoeconomic analyses go beyond comparison of drug acquisition cost, to evaluate a drug's impact on total institutional expenditures for patient care. Such analyses allow for the evaluation of all costs associated with drug therapy.

Pharmacoeconomic research is primarily driven by the basic principle that financial resources are limited and that the organisational needs generally exceed available resources (Waning & Montagne, 2001:143). It therefore identifies, measures and compares the cost and consequences of pharmaceutical products and services. More specifically, pharmacoeconomic research involves identifying, measuring and comparing the costs, risks and benefits of programmes, services or therapies and determining which alternative produces the best health outcome for the resources invested (Jolicoeur, *et al.*, 1992:1741).

3.4.2 The aim of pharmacoeconomics

According to Bloom (Lombard, 2000:56) the aim of pharmacoeconomic analysis is to improve public health through improved rational decision-making, entailing the selection of one alternative among several others, by determining which alternative produces the best outcome for the resources invested.

3.4.3 The importance of pharmacoeconomics

Pharmacoeconomic research is important because it comprises the analytical approach to identifying, measuring and comparing the consumption of resources and to analyse and describe the consequences of consumption (Truter, 1997:19).

Waning and Montagne (2001:143) state that pharmacoeconomic research is important because it helps

- provide data on making critical decisions, such as determining which drugs should be on the organisation's formulary;
- define the best organisational strategy for managing a particular disease state;
- select the most appropriate agent to treat a patient's medical condition;
- administrators and other managers to decide which service to implement within their organisation; and
- provide valuable information that is used by a number of health-care decision-makers.

3.4.4 Applications of pharmacoeconomics

Brown (quoted by Badenhorst 2002: 84) states that pharmacoeconomics has become a key factor in the marketing mix. Analysis of new products, within their respective 'protocols of care', provides 'third party testimony' that assists in the evaluation of the new medicine and helps justify increased cost through saving in the total healthcare budget. This analysis needs to be used at all stages of the purchasing process, e.g. to influence government agencies and gain reimbursement, to influence the policies of third party payers and to influence the prescribing behaviour of physicians, either directly or via the inclusion of the product within agreed 'protocols of care'.

3.4.5 Dimensions of pharmacoeconomic analysis

According to Malek (1996a: 760), the three fundamental dimensions of pharmacoeconomic studies include the following:

- The perspective of the analytical study.
- The types of cost.
- Outcomes used.

3.4.5.1 Analytical perspective

The perspective of a pharmacoeconomic study is the point of view from which it is conducted. A study may be performed from the perspective of a hospital or another healthcare provider, a payer, a patient, or society in general. It is important to understand the study perspective because it determines which outcomes and cost will be measured. Consequently, the study perspective directs and limits how the results are interpreted and applied. Therefore, in assessing any pharmacoeconomic study, one should first determine from which perspective the study is conducted (Waning & Montagne, 2001:147).

As stated previously, the study may be performed from various perspectives:

Patients are generally concerned with how treatment will affect their family's quality of life. The patient is also concerned that the medication he / she receives is of good quality with proven efficacy and safety and continuously available at an affordable price.

Providers, hospital or healthcare systems are, on the other hand, primarily concerned with the benefits to their organisations.

As said by Eisenberg (quoted by Lombard, 2000:57) the cost to the provider is the true cost of providing the service, while the cost to the payer is the cost allowed by that payer. The cost to the patients is the amount they pay for the service (that is the portion not covered by the third party or medical aid) plus the other costs incurred due to the illness.

3.4.5.2 The type of cost and outcome used

(i) Evaluation of costs in pharmacoeconomic analysis

A pharmacoeconomic analysis should compare all the relevant treatments for a given treatment indication of the drug under study. The comparators should include at least the drug or medical treatment that is most commonly in use, as well as the others for which it may be a substitute. The approach to enumerating the cost and valuing it is fundamentally the same for each type of pharmacoeconomic analysis (Freund & Dittus, 1992:24, 25).

The concept of cost deals with resources that are used or consumed in the production of goods or services. In the process, several services may be used: prescription drugs, laboratory tests, hospital stays, physician visits, and surgical procedures. These services require basic resources such as personnel, equipment, facilities and supplies. To determine the cost associated with particular goods or services, units of resources used must be determined and the associated cost of the resources calculated (Struwig, 2000:58).

(ii) Costs

- **Cost** is the magnitude of resources consumed. The cost of a product or a service is the monetary value of resources consumed in its production or delivery. Resources include labour, plant equipment, and supplies (Larson, 1996:46).

- A **fixed cost** is a cost that does not vary with the quantity or volume of output provided in the short run. These costs usually vary with time, but not with quantity or volume of service provided, and may include rent, equipment, lease payments, and some wages and salaries. The cost of maintaining an outpatient clinic is fixed, regardless of the number of patients (Struwig, 2000:59).

- **Variable costs** are those costs that vary with changes in output or volume. Examples include drugs, devices and suppliers. The pharmaceutical expenditure in the outpatient clinic, as mentioned above, will rise if more patients are seen, i.e. if there is a greater output (Struwig, 2000:58, 59).

- **Direct medical costs** are those costs incurred for medical products and services used to prevent, detect and or treat a disease. These costs may be fixed or variable (Sanchez, 1997:3).

- **Direct non-medical costs** are those costs that are incurred as a result of the illness but which do not involve purchasing of medical services (Sanchez, 1997:3).

- **Indirect costs** include the costs that result from changes in production capacity brought about by the drug or other health interventions under study. For example, one drug in comparison to another may return someone back to work sooner or may result in more days lost from normal activities (Freund & Dittus, 1992:25).

- **Intangible costs** are the costs or savings associated with additional or lessened pain and suffering attributable to a new medical intervention or drug. In spite of the fact that it is difficult to quantify, intangible costs are regarded as important (Freund & Dittus, 1992:25).

- **Average costs** are the resources consumed per unit of output (Struwig, 2000: 59).

- **Marginal costs** are the change in total cost of producing one additional (or one less) unit of output. Because fixed cost remains unchanged as output increases, marginal costs may be viewed as the average variable cost (Larson, 1996:46).

- **Opportunity costs** represent the economic benefit forgone when using one therapy instead of the next best alternative therapy (Sanchez, 1997:3).

TABLE 3.8

Characteristics of costs used in economic evaluations (Malek, 1996b:5)

COST	DESCRIPTION
Total costs	• Costs of all resources necessary to produce any particular level of output. • Increases with output, because obtaining more output always requires more input, irrespective of the scale of production. • Can be divided into 2 components, namely fixed and variable costs
Fixed cost	• Costs that remain unchanged over a range of output in the short term. • The cost that an organisation incurred whether it is producing nothing at all, one unit, or its maximal possible capacity.
Variable costs	• Costs that vary with the scale of production. • Increase as output rises, since the need for labour, raw material etc. increases. • Is zero in absence of output, unlike fixed costs.
Average costs	• The total cost divided by the number of units produced.
Marginal costs	• The costs associated with the production of one additional unit of a commodity.

(iii) Outcomes

Waning and Montagne (2001:144) state that in pharmacoeconomic research, an outcome is a consequence of drug therapy intervention. The primary drug therapy outcomes that pharmacoeconomic research typically evaluates are clinical outcomes, human outcomes and economic outcomes.

a) **Clinical outcomes** include the results of treatment with a drug and may be both favourable and unfavourable. For example, a drug may cure, prevent or slow the progression of a disease (a favourable outcome) but also have serious side-effects or toxicity associated with it (an unfavourable outcome). Therefore, when pharmacoeconomic studies develop clinical

outcome measures, investigators must consider all potential consequences of a therapy, not only the benefits.

b) **Human outcomes** look at a therapy from the patient's point of view. These outcomes address such questions as what the patient feels like and what he/ she perceives his /her quality of life to be. A drug that prolongs a patient's life may not be considered beneficial by the patient if he or she believes quality of life has become sub-optimal. For instance, a patient with a catastrophic illness may not value a drug that prolongs his or her life in the same way that a patient with a less serious medical problem would. Therefore, human outcomes are very important in assessing the overall value of a medication.

c) **Economic outcomes** are the costs associated with a therapy. These costs were discussed under costs above.

TABLE 3.9

Components of pharmacoeconomics (Sanchez, 1997:4).

Economic evaluation	**Human evaluation**
• Cost of illness • Cost minimisation • Cost benefit • Cost- effectiveness • Cost utility	• Quality of life • Patient preference • Patient satisfaction

3.5 TYPES OF PHARMACOECONOMIC ANALYSES

Malek (1996a: 761) states that the purpose of an economic evaluation is to provide a menu of choices together with a comparison between cost and outcomes associated with each choice. A full economic analysis will always consider all costs and consequences of all viable alternatives. The main difference between the methods used in pharmacoeconomic analysis is the nature of the outcome measured.

The basic task of economic evaluation is to identify, measure, value and compare the costs and consequences of the alternatives being considered. There are two distinguishing characteristics when doing a pharmacoeconomic evaluation. Firstly, it is whether there is a comparison between two or more alternatives and secondly, whether both cost and consequences of the alternatives are being examined. A full economic evaluation encompasses both characteristics, while a partial evaluation addresses only one of these characteristics (Sanchez, 1997: 4).

There are four common types of pharmacoeconomic evaluations. Each of these studies measures costs in rands, but there are differences in how the outcomes are valued. An understanding of these various types of studies is important for the most appropriate interpretation of the results (Waning & Montagne, 2001: 147).

The four types of economic analyses differ primarily in whether therapeutic consequences are measured in monetary terms cost benefit analysis (CBA), physical units cost effectiveness analysis (CEA), or measures of quality of life cost utility analysis (CUA), or are assumed equal cost minimisation analysis (CMA) (Freund & Dittus, 1992:22). Further details of these techniques are discussed below.

3.5.1 Cost minimisation analysis

The first type of pharmacoeconomic analysis is a cost minimisation analysis, which is the most basic of the research methodologies. A cost minimisation analysis simply compares the cost of two or more alternatives, assuming equal outcomes of each alternative (Waning & Montagne, 2001:147).

For CMA to be the appropriate technique, the outcomes of using one drug versus another, or a drug versus a different medical treatment, must be clinically identical in similar patients (i.e., clinical effectiveness must be the same for both treatments) (Freund & Dittus, 1992:22).

Because of the strict requirements of therapeutic equality, cost minimisation analysis is not commonly used to assess drug therapies, programmes or services. This method could, however, be useful when assessing the cost difference among dosage forms of the same drug or among generically equivalent drugs for which patient outcomes have been shown to be the same (Jolicoeur *et al.*, 1992:1741).

3.5.2 Cost benefit analysis

Cost benefit analysis (CBA) is a basic tool that can be used to improve the decision-making process in the allocation of funds to a healthcare problem. Although the general concept of CBA is not overly complicated, many technical considerations require a degree of explanation and interpretation in order to understand how it can be or has been applied. Cost benefit analysis consists of identifying all the benefits that accrue from the programme or intervention and converting them into rands in the year in which they will occur. This stream of benefit rands is then discounted to its present value at the selected interest rate (Bootman *et al.*, 1996:10).

When all the outcomes are converted to rand values, the benefit to cost ratio of the net costs or benefits can be directly compared so that the alternative with the greatest benefit can be chosen (Freund & Dittus, 1992:24).

On the other side of the equation, all programme costs are identified and allocated through a specific year, and, again, the costs are discounted to their present value. If all relevant factors remain constant, the programme with the largest present value of benefits less costs is the best in terms of its economic value. Ideally, all benefits and costs resulting from the programme should be included. This presents considerable difficulty, especially on the benefits side of the equation, as many benefits are either difficult to measure, difficult to convert to rands, or both. A cost benefit analysis has often been used when comparing the value of dissimilar programmes where the outcomes are in different units (Bootman *et al.*, 1996:10).

3.5.3 Cost-effectiveness analysis

Like cost benefit analysis, cost-effective analysis (CEA) is an approach used for identifying, measuring and comparing the significant costs and consequences of alternative interventions. 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 type of non-drug treatment for a particular condition (Chrischilles, 1996:79).

In cost-effective analysis, the outcomes of the alternatives are not measured in monetary units, but rather in natural or physical units (e.g. years of life saved, complication avoided). Although a CEA does not assume equal outcomes, it should compare alternatives with similar objectives (e.g. prevention or treatment of disease) (Waning & Montagne, 2001:149).

Unlike CBA, which values all effects of an intervention in monetary terms, CEA measures some effects in non-monetary terms. For this reason, some believe that CEA is less comprehensive than CBA, since it excludes the evaluation of life (Chrischilles, 1996:79).

In CEA, analytical results are summarised by the ratio of cost to effectiveness (C/E). After the (C/E) ratios for competing drugs or therapies have been determined, comparisons can be made among alternatives using the average C/E ratios (each new drug compared to the baseline standard therapy) or marginal C/E ratios (the incremental cost-effectiveness of each alternative therapy). In general, marginal cost-effectiveness analysis is appropriate (Freund & Dittus, 1992:23).

One of the limitations of CEA is that treatment strategies (whether a drug or another form of treatment) often cannot be compared across diseases or programmes (Freund & Dittus, 1992:23).

Jolicoeur *et al.* (1992:1741) state that cost-effectiveness alternatives are not by definition the least expensive. A treatment can be considered cost-effective if it includes the following:

- Less expensive and at least as effective as other alternatives.
- More expensive than alternatives with additional benefits worth the additional cost.
- Less expensive and less effective in instances where extra benefits are not worth the extra cost.

3.5.4 Cost utility analysis

Cost utility analysis (CUA) is a method that accounts for effectiveness while integrating patient preferences and satisfaction. This method, unlike CEA, evaluates outcomes not only for the associated monetary cost but also for the added cost of patient discomfort or changes in function or level of satisfaction (Jolicoeur *et al.*,1992: 1743).

Cost utility analysis measures costs of an intervention in monetary units and outcomes in terms of the value that patients gain from medical therapy. Rather than expressing outcomes in terms of objective clinical measure, a cost utility analysis is concerned with patients' subjective valuations of the benefits they receive from therapy (Schulman & Linas, 1997:532).

CUA takes advantage of the normative theory of rational decision-making under conditions of uncertainty. It is the only method available for simultaneously synthesising multiple outcomes into a single measure (such as the impact of drug on both morbidity and normality, or the impact of drugs on both pain and physical functioning) in a formal economic evaluation. Such a synthesis is possible because each outcome is weighed in the analysis by a person's preference for experiencing the outcome. These weights, or preferences, are formally known as utilities (Freund & Dittus, 1992:23).

No standards criteria have been established for measuring utilities. Criteria are generally determined by healthy individuals and therefore cannot be generalisable to patients. A more individualised method of incorporating the quality of life measurements into economic evaluations may better present patient preference (Jolicoeur *et al.*, 1992:1742).

3.5.5 Cost of illness

The cost of illness is the sum of:

I. The medical resources used to treat the illness, for example:

- Hospital care
- Professional services
- Drugs
- Supplies

II. The non-medical resources associated with it, for example:

- Transportation to the premises of treatment
- Lodging for the family during treatment
- Hiring of a person to help with home-care

III. The loss of productivity due to illness or disability.

(Adapted from Bootman *et al.*, 1996:12).

The components can be summarised by table 3.10.

TABLE 3.10

Summary of pharmacoeconomic components

(Adapted from Sanchez, 1999:3)

Method	Description	Application	Cost (unit)	Outcome unit
Cost minimisation analysis (CMA)	Finds the least expensive cost alternatives	Used when outcomes are the same	Rand	Assumes to be equivalent
Cost benefit analysis (CBA)	Measures benefit in monetary units and computes a net gain	Can compare programmes with different objectives	Rand	Rand
Cost effectiveness analysis (CEA)	Compares alternatives with therapeutic effects measured in physical units; computes a C/E ratio	Can compare drugs/programmes that differ in clinical outcomes and use same unit of benefit	Rand	Natural units
Cost utility analysis (CUA)	Measures therapeutic consequences in utility units rather than physical units; computes a C/U ratio	Used to compare drugs/programmes that are life-extending with serious side-effects or those producing reductions in morbidity	Rand	Quality – adjusted life years gained
Cost of illness	Estimates the cost of a defined population	Used to provide baseline to compare prevention /treatment options	Rand	Not available

3.5.6 Conducting a pharmacoeconomic study

Dao (quoted by Badenhorst 2002: 95) states that, from a practical point of view, the application of CBA, CEA, and quality of life assessment to a drug begins with the identification of a competitor for comparison purposes. The profile of the drug is then assessed against that of the competitor. The parameters to be considered include:

- Safety or side-effects
- Efficacy
- Dosing regiment
- Dosage form
- Delivery system
- Legal status
- Price

A drug's superiority in terms of its side-effects, dosage form (e.g. liquid form is preferred to tablets by some elderly population), dosing regimen (e.g. once a day vs. three times a day) and delivery system (e.g. transdermal vs. intramuscular injections) would mean better compliance, which in turn affects the drug's perceived efficacy and its cost effectiveness. In addition, differences in dosage form, dosing regimen, and delivery system also affect the cost of administering the drugs.

3.5.7 Limitations to pharmacoeconomic analysis

The economic analysis remains a model of the anticipated consequences of alternative decisions. While such models are capable of facilitating decision-making, the responsibility of individuals for making decisions is not diminished. Nevertheless, the power of the analytical techniques provides ample justification of those faced with resource allocation decisions to come to terms with the principle of economic analysis (Freund & Dittus, 1992:28).

3.6 CONCLUSION

Pharmacoeconomic studies can provide valuable information about the cost and consequences of pharmaceutical products and services, and can assist healthcare decision makers in optimising the allocation of scarce resources by providing guidance on when and where to use a particular pharmaceutical product.

3.7 CHAPTER SUMMARY

The concepts and approaches of healthcare and cost analysis were discussed in this chapter. The definition, aim, reasons and applications of pharmacoepidemiological studies were discussed. Pharmacoeconomics were discussed according to the definition, aim, application, and different methods.

Because of the increasing attention paid to the growing costs of healthcare, pharmacoepidemiology and pharmacoeconomics must undoubtedly be extensively used in order to plan and evaluate the developments in containment of drug expenditure.

CHAPTER 4

EMPIRICAL INVESTIGATION

4.1 INTRODUCTION

In this chapter, the empirical investigation will be discussed as follows:

- The aims and objective of the study.
- The research design.
- The research methodology.

4.2 OBJECTIVES OF THE EMPIRICAL INVESTIGATION

The general objective of the cost analysis study was to review and analyse the cost of ACE inhibitor items by using a medical aid claims database.

The specific objectives pertaining to this study were to

- conceptualise the use of ACE inhibitors in the treatment of hypertension and congestive heart failure from available literature;
- investigate the methods and techniques that are utilised in health-care, in order to ensure cost-effective drug use from available literature;
- review the total cost of ACE inhibitor items derived from the database;
- determine the prevalence and usage patterns of ACE inhibitors as well as the costs associated with these drugs from the database;
- identify and analyse the different innovator forms of ACE inhibitors with their different generic equivalents from the database;
- determine the prevalence and costs associated with innovator and generic drugs of the ACE inhibitor agents from the database; and

- identify combination (mono or double) therapy of ACE inhibitor items and to determine the costs associated with these combinations from the database.

NB. An item refers to a medicine product that contains an ACE inhibitor in a single dose form or an ACE inhibitor combined with another medicinal drug in a combination product as a single entity.

4.3 RESEARCH DESIGN

The research design of the study was done by dividing all the ACE inhibitor items in the database into chemical categories and then separating them into the individual active ingredient and its equivalent generics.

4.4 RESEARCH METHODOLOGY

4.4.1 Data source

The data were obtained from the central database of Interpharm Data Systems (Pty.) Ltd. Interpharm® (IDS). IDS was bought by Medscheme with 100 % ownership and board representation. It operates as a separate (Pty) Ltd company with its own board of directors. IDS is responsible for the prescription claims processing of more than 50% of the private health care market in South Africa (Serfontein: 2003).

Data for the study population consisted of all prescriptions containing one or more ACE inhibitor items as extracted from the central Database of Interpharm datasystems® for a period of one year, from 1 January 2001 to 31 December 2001.

4.4.2 Study population

4.4.2.1 Selection of the study population

The study population was selected according to the prescriptions analysed on the medicine claims database (as mentioned in paragraph 4.4.1.). All prescriptions, containing an item or items classified as ACE inhibitors were selected for the analyses.
A total of 1 475 532 prescriptions containing a total of 2 953 244 ACE inhibitor items represented the study population. This data will be analysed and discussed according to different criteria selected for the purpose of this study (see the paragraph below).

4.4.2.2 Selection of criteria for the data analysis

The four criteria selected for the data analyses are the following:

- Chemical categories of ACE inhibitors.
- Different active ingredients.
- Original or generic equivalents.
- Different dosage quantities (strength) of an original drug and its generic equivalents.

All data collected from the selected N = 1 475 532 prescriptions will be analysed according to these four criteria.

4.4.3 Data analysis

Data were analysed according to the classification system and software used.

4.4.3.1 Classification systems

For this study, the category system according to Mignat and Unger (1995:335) was used, (refer to paragraph 2.2.4). Every agent was analysed according to the National Approved Product

Pricing Index (NAPPI) code, which was also used to distinguish between different dosage quantities of the drugs:

- The NAPPI code

Every agent on the medicine claims database has a NAPPI code. The NAPPI code consists of a series of numbers, which is unique for every agent and which also distinguishes between different dosage forms of the same agent. The NAPPI codes of the ACE inhibitor items were used to acquire the data from the central database, run the queries in SAS 8.2® as well as to distinguish between the different dosage forms.

(i) Chemical classification

This form of classification was utilised in the literature review as well as in the empirical investigation. For the purpose of the empirical investigation the ACE inhibitor items were categorised in one of the following four chemical groups (refer to table 2.1):

- Carboxyl-Enalapril
- Sulphydril-Captopril
- Phosphonyl-Fosenopril
- Combinations-Benazepril+Hydrochlorothiazide

(ii) Active ingredient classification

Due to the fact that the category classification only constitutes four groups, thus having extremely large categories, the ACE inhibitor items were also analysed according to twenty typical product items (some containing an ACE inhibitor in combination with another drug).

(iii) Classification according to original or generic drug

This is another interior under which ACE inhibitors will be analysed, whether it is an original or a generic drug.

(iv) Different dosage quantities (strength)

4.4.3.2 Software used

The software that was used in this study period for the analysis of the data:

- Microsoft® word 97 SR-2.
- SAS® 8.2 computer package (SAS Institute Inc., 2002) for the collection and statistical analysis of data, which was executed on the Windows® 2002 platform.
- Microsoft® excel 97.

4.5 MEASURING CRITERIA

4.5.1 Aspects/entities for measurement

The following aspects/entities will be analysed for each ACE inhibitor classification:

- Dosage quantity
- Prevalence
- Costs

4.5.1.1. Dosage quantity

The dosage quantities (strengths) prescribed for this analysis will be discussed under the different innovator and generic classifications.

4.5.1.2 Prevalence

The prevalence in this study is the first step to analysis, as it will help in determining the popularity in prescribing patterns.

4.5.1.3 Cost

With regard to the literature, the cost of a product or a service can be defined as the monetary value of the resources consumed in its production or delivery (Larson, 1996:46).

In this study the total cost, the average medicine cost, the minimum and maximum treatment cost, the d-value and the cost index of ACE inhibitors will be analysed as follows:

- Total cost of ACE inhibitor product items on the entire database.
- The differences in the total cost of four different therapeutic categories of ACE inhibitors.
- Cost implications of most frequently prescribed items of each therapeutic category.
- Total cost differences of twenty different typical product items containing ACE inhibitors.
- Total cost difference of innovator and generic drugs.
- Cost implications of different dosage quantities.

4.6 STATISTICAL ANALYSIS

The following statistical methods were used to analyse the data according to the measuring criteria as discussed in paragraph 4.5.

4.6.1 Average value (mean)

Brase and Brase (1999:94) state that an average that uses the exact value of each entry is the mean (also called the arithmetic mean). To compute the mean, the sum of all the entries are divided by the number of entries. The following equation is used for the calculation:

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

Where :

x = the values of the variable.

$\sum$ = the sum of.

n = the number of observations.

4.6.2 Standard deviation

The standard deviation is a measure of variation and is defined as the differences/deviation of values from the mean (average) value. It indicates how many values in a distribution differ from the mean, or how representative the mean is of the total distribution (Walley & Haycox, 1997:346).

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

Where

s = standard deviation.

n = the number of observations.

$\bar{x}$ = the mean.

x = any value in the data set.

4.6.3 Cost index

The following equation is used for the calculation of cost index (Serfontein,1989:180):

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

In context of the study, the cost index can be interpreted as follows:

- If cost index is greater than 1, then the therapy utilised is relatively expensive.
- If cost index is equal to 1, then there is equilibrium between the costs and prevalence of the therapy.
- If cost index is less than 1, then the therapy utilised is relatively inexpensive.

4.6.4 Effect sizes/ "d"-value

Effects sizes (d) can be defined as the degree to which the phenomenon is present in the population (Cohen, 1969:210). For the purpose of this study the d-value or the effect sizes will be used to determine whether there were practically significant differences between prescribed average medicine treatment costs. The d-value (practical significance) is calculated by using the following formula:

$$d = \frac{(\overline{x_a} - \overline{x_b})}{S_{max}}$$

where:

$\overline{x_a}$ = the average medicine treatment cost of a.

$\overline{x_b}$ = the average medicine treatment cost of b.

S_{max} = the maximum standard deviation between a and b.

Steyn (1998:3) recommends the following guidelines for practical significance:

$d = 0.2$: small effect – non-significant

$d = 0.5$: medium effect - observable and may be practically significant

$d = 0.8$: large effect - significant and of practical importance

4.7 RELIABILITY AND VALIDITY

The data for analysis were obtained from a medicine claims database. The research was conducted assuming that all data would be correct.

The data obtained and analysed from the data source can only be generalised to the database and the specific study population.

4.8 REPORT AND DISCUSSION

The discussion and conclusion of the results of the empirical investigation will follow in Chapter 5.

4.9 RECOMMENDATIONS

The recommendations of the empirical investigation will be discussed in Chapter 6.

4.10 CHAPTER SUMMARY

The objective of the empirical study, data source, database, and methodology were discussed in this chapter.

In Chapter 5 the analysis, the results and the empirical investigation will be discussed.

CHAPTER 5

RESULTS AND DISCUSSION

5.1 INTRODUCTION

In this chapter, the results of the empirical investigation conducted for the period 1 January 2001 to 31 December 2001 will be discussed. The data utilised in the empirical investigation have been derived from a medical aid claims database.

5.2 GENERAL MEDICINE UTILISATION PATTERNS

The ACE inhibitor items that were identified from the central medicine claims database, (during the period of the study), are summarised according to the following: the four categories, the different active ingredients, innovator or generic classification and their different dosage quantities (strengths).

An analysis on the usage patterns and costs of ACE inhibitors will be based on the ACE inhibitor items listed in table 5.1. Please note that the ACE inhibitor items listed are all agents that were available on the South African market, which appeared on the central medical aid claims database during the period of analysis. Any medicinal agents that became available after 31 December 2001 will not be included in the analysis.

Table 5.1. Classification of ACE inhibitor items according to four different chemical categories (A-D).

A. Carboxyl	B. Sulphydril	C. Phosphonyl	D. Combination
1. Enalapril	9.Captopril	10.Fosenopril	11.Benazepril + hydrochlorothiazide
2. Lisinopril			12. Trandolapril + verapamil hydrochloride
3. Cilazapril			13. Fosenopril + hydrochlorothiazide
4. Perindopril			14. Captopril + hydrochlorothiazide
5. Quinalapril			15. Quinalapril + hydrochlorothiazide
6. Ramipril			16. Perindopril + indapamide
7. Benazepril			17. Cilazapril + hydrochlorothiazide
8.Trandolapril			18. Lisinopril + hydrochlorothiazide
			19. Enalapril + hydrochlorothiazide
			20. Ramipril + felodipine

*The typical product items are numbered (1-20), and consist of single items and combination ACE inhibitor items.

The results of the general medicine utilisation patterns, derived from the medicine claims database, are tabulated in table 5.2. From this point onwards, hydrochlorothiazide will be written as its abbreviation *HCTZ*.

Table 5.2 Medicine items in the total database.

Description	*Total item population*
Number of prescriptions	1 475 532
Total number of items prescribed	2 953 244 *
Median	2.00
Average number of items per prescription	2.00 ± 1.17
Minimum number of items per prescription	1
Maximum number of items per prescription	17
Total cost (R)	379 911 472.00
Cost median (R)	87.36
Average cost per item (R)	128.64 ± 151.97
Minimum cost per item (R)	-
Maximum cost per item (R)	-

*The amount of the total number of ACE inhibitor items prescribed on the database does not include medical equipment and mixtures. This was because our research was focused only on the medicinal items on the database.

1 475 532 prescriptions were issued during the study period (1 January 2001 to 31 December 2001), 68162 of the prescriptions contained ACE inhibitor items which constituted 4.62% of all prescriptions issued during the twelve-month period. According to table 5.2, the total number of items prescribed was 2 953 244, (excluding mixtures and non medicinal items) with 68 162 (2.31%) of these items identified as ACE inhibitor items.

A cost value of all ACE inhibitor items on the database was calculated, which amounted to R13 863 080.90, constituting 3.65% of the total cost (R379 911 472.00) of all the medicine items on the database.

5.3 THE PREVALENCE AND COST ANALYSIS OF ACE INHIBITOR ITEMS

The prevalence and costs of ACE inhibitor items were ascertained from computerised records of the medical aid claims database of prescriptions issued during the specific study period and will be discussed according to the four-fold classification of ACE inhibitors namely:

- The four chemical categories,
- The twenty typical ACE inhibitor items,
- The innovator or generic ACE inhibitor items,
- The dosage quantities (streghth) of the innovator and its generics.

5.3.1 Prevalence and cost of ACE inhibitor items based on the chemical category classification.

Table 5.3 is a summary of the prevalence and cost of ACE inhibitor items, the prevalence percentage and cost percentage of ACE inhibitor items as well as the cost indexes of ACE inhibitor items based on the different categories.

The prevalence and cost percentages are illustrated in figure 5.1. and were calculated by dividing the number of ACE inhibitor items of a specific category (A) by the total prevalence of all ACE inhibitor items (n =68 162) and then multiplying by a hundred. (e.g. prevalence percentage for Carboxyl category (A): (39 522 ÷ 68 162) x 100 = 57.98%).

It is important to note that all amounts have been rounded off to two decimal points throughout the results and discussion chapter. In some cases in the chapter the amounts will be given in three decimal points since the values are too small and this is done to avoid miscalculations. Thus the sum of the percentage totals will not always amount to one hundred percent (as is the case in table 5.3).

Table 5.3 Prevalence, cost and cost index values of ACE inhibitor items based on the categories.

Category Classification	Number of ACE inhibitor items	Prevalence of ACE inhibitors (n=68162) (%)	Cost of ACE inhibitors (R)	Cost of ACE inhibitors (n=R13863080.90) (%)	Cost index
Category A	39522	57.98	7707056.50	55.59	0.96
Category B	4486	6.58	582483.36	4.20	0.64
Category C	882	1.29	157519.93	1.14	0.88
Category D	23272	34.14	5416020.79	39.07	1.14
Total	68162	99.99*	13863080.90	100	

*The sum of the percentage column does not amount to 100 due to the fact that amounts were rounded off to two decimal points.

The cost percentages were calculated in a similar manner to the prevalence percentages, by dividing the cost of ACE inhibitor items for a specific category (A) by the total cost of all ACE inhibitor items and then multiply by a hundred (n =R7 707 056.50). (e. g. cost percentage for ACE inhibitor items: (R7 707 056.50 ÷ R13 863 080.90) x 100 = 55.58%.

Figure 5.1 Prevalence and cost percentages of ACE inhibitor items based on the chemical categories.

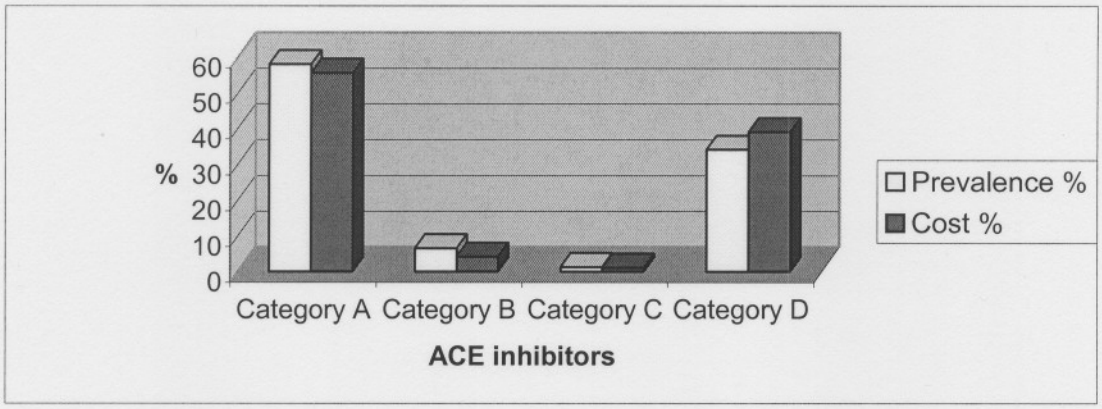


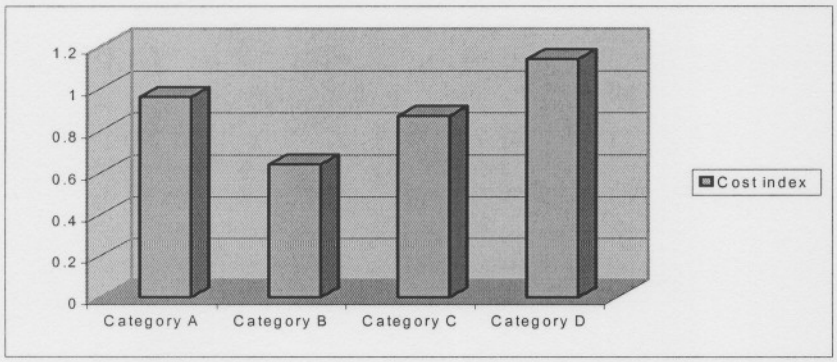
Figure 5.1 indicates that category A represents the largest proporion of ACE inhibitor items use, amounting to a prevalence (number of ACE inhibitor items prescribed) of 39 522 (57.98%; n =68 162) with the cost thereof representing R7 707 056.50 (55.59%; n = R13 863 080.90).

Category D is the only category with the cost value which is greater than the prevalance value. It has the second largest prevalence and cost percentage values, the prevalence being 23 272 (34.14%; n = 68 162) with a cost of R5 416 020.79 (39.07%; n = R13 863 080.90).

Of the four categories, category B is the third category that is larger, though very small compared to the first two categories A and D in prevalence and cost. The prevalence being 4 486 (6.58%; n = 68 162) with the cost of R582 483.36 (4.20%; n =. R13 863 080.90). Category C is the group with the lowest prevalence representing 882 (1.29%; n =68 162) as well as, the lowest cost representing R157 519.93 (1.13%; n =R13 863 080.90). As said above, the cost of category D exceeds the prevalence of this group with a difference between prevalence percentage and cost percentage of 4.93%, thus its cost is greater than its prevalence. The prevalence percentage of the other three categories A, B and C exceeds the cost percentage, thus indicating that, of the four categories, category D has the most effect on the cost of ACE inhibitor treatment. This statement is emphasised by the cost index values, where only category D has a cost index value above one (refer to fig 5.2).

Note from paragraph 4.6.4 that if the cost index value is greater than 1 then the therapy utilised is relatively expensive. As thus category D ACE inhibitor items have an index value greater than 1 implying that they are relatively expensive.

Figure 5.2 Cost index values of ACE inhibitor items based on the chemical categories.



5.3.2 Prevalence and cost of twenty typical ACE inhibitor items

As shown in table 5.4, Perindopril represents the active ingredient with the highest prevalence 10 297 (15.11%; n =68 162) for the twelve-month period and also constitutes the highest cost R2 197 237.70 (15.85%; n = R13 863 080.90) of all the ACE inhibitor items present on the database.

The prevalence of Perindopril when compared to the prevalence of 8 635 Enalapril (12.67%; n =68 162), Ramipril, with a prevalence of 7 997 (11.73%; n =68 162) and Lisinopril, with the prevalence of 7 784 (11.42%; n = 68 162), which represents the active ingredients with the second, third, and fourth largest prevalence, is fairly high. The extensive use of Perindopril is emphasised by the fact that it is one of the first ACE inhibitors that were ever manufactured. Moreover, when comparing the cost indexes of the twenty ACE inhibitor items, presented in table 5.4, it was found that the cost index of half the ACE inhibitor items exceeds one, thus indicating that ACE inhibitors are relatively expensive.

Table 5.4 Prevalence, cost and cost index values of twenty typical ACE inhibitor items.

Active ingredient classification (ACE inhibitor item)	Number of ACE inhibitor items	Prevalence of ACE inhibitors (n=68 162) (%)	Cost of ACE inhibitors (R)	Cost of ACE inhibitors (n=R13 863 080.90) (%)	Cost index
1. Enalapril	8 635	12.67	1 698 118.30	12.25	0.97
2. Lisinopril	7 784	11.42	1 136 944.07	8.20	0.72
3. Cilazapril	551	0.81	86 356.37	0.62	0.77
4. Perindopril	10 297	15.11	2 197 237.70	15.85	1.05
5. Quinalapril	3 382	4.96	575 995.37	4.15	0.84
6. Ramipril	7 997	11.73	1 770 577.53	12.77	1.09
7 Benazepril	139	0.20	23 600.05	0.17	0.85
8.Trandolapril	737	1.08	218 227.11	1.57	1.39
9.Captopril	4 486	6.58	582 483.68	4.20	0.63
10.Fosenopril	882	1.29	157 519.93	1.14	0.88
11.Benazepril + HCTZ	92	0.13	21 772.63	0.16	1.23
12. Trandolapril + verapamil HCl	1 508	2.21	462 908.28	3.34	1.51
13. Fosenopril + HCTZ	398	0.58	84 657.48	0.61	1.05
14. Captopril + HCTZ	1 104	1.62	196 793.01	1.42	0.88
15. Quinalapril + HCTZ	6 040	8.86	1 137 499.12	8.21	0.92
16.Perindopril + indapamide	1 622	2.38	379 720.97	2.74	1.15
17. Cilazapril + HCTZ	404	0.59	81 070.16	0.58	0.98
18. Lisinopril + HCTZ	5 642	8.28	1 324 955.26	9.56	1.15
19. Enalapril + HCTZ	4 779	7.01	1 316 596.28	9.50	1.35
20. Ramipril + felodipine	1 683	2.47	410 047.60	2.96	1.20
Total	68 162	99.98	13 863 080.90	100	-

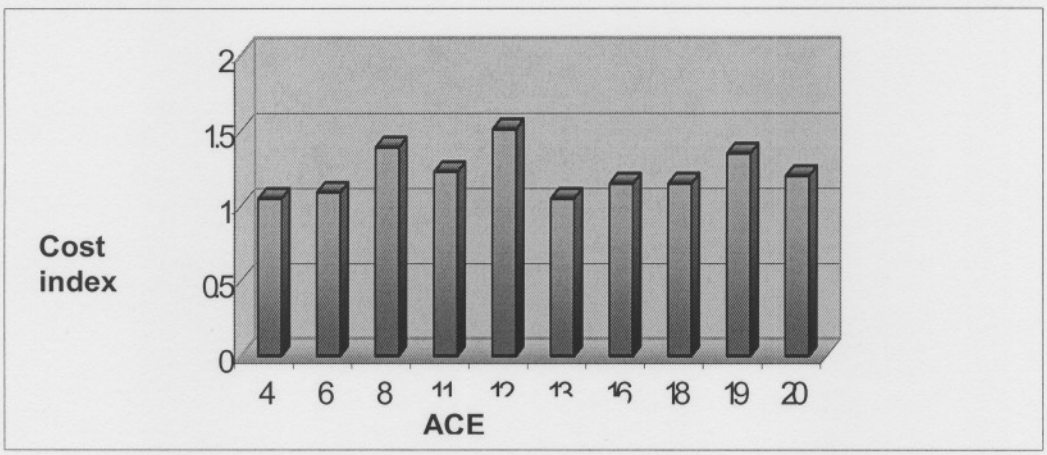
*The sum of the percentage columns does not amount to 100 due to the fact that amounts were rounded off to two decimals.

Numerical values have been awarded to the active ingredients to ensure clarity and are as stated from 1-20 above. Figure 5.3 is an illustration of the cost index values of ACE inhibitor items according to the active ingredient classifications that are higher than one. Of all the ACE inhibitor items, ten had a cost index value greater than 1 indicating a relatively high cost in comparison with prevalence.

The cost prevalence index analysis will be on the numerical values (1- 20) of the ACE inhibitor items (refer to table 5.4). Only the drugs with a cost index values greater than one will be analysed here (figure 5.3):

4. Perindopril
6. Ramipril
8. Trandolapril
11. Benazapril + HCZT
12. Trandolapril + Verapamil HCl
13. Fosenopril + HCZT
16. Perindopril + Indapamide
18. Lisinopril + HCZT
19. Enalapril + HCTZ
20. Ramipril + HCTZ

Figure 5.3 Cost index analysis of ACE inhibitor items with a value exceeding one based on the active ingredient classification.



5.4. COST ANALYSIS OF ACE INHIBITOR ITEMS

5.4.1 Cost analysis of ACE inhibitor items according to the chemical category classification.

Table 5.5 Cost analysis of ACE inhibitor items according to the four chemical categories.

SNYMAN(2002: 135) classification	Frequency of ACE inhibitor-items (n)	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Category A	39 522	195.00	76.20	0.74	840.99
Category B	4 486	129.84	102.64	0.33	654.34
Category C	882	178.59	46.69	57.68	436.32
Category D	23 272	232.82	62.77	0.31	608.55
TOTAL	68 162	-	-	-	-

A comparison of the average cost of the different categories as depicted in table 5.5 indicates the following:

Category D (combination category) has the highest average cost (R232.82 ± R62.77), Category A (carboxyl) has the second highest average cost (R195.00 ± R76.20), Category C (sulphydril) has the third highest average cost (R178.59 ± R4 6.69) and Category B (phosphinyl) has the lowest average cost (R129.84 ± R102.64).

A possible explanation for the considerably high average cost of the category D can be due to the fact that this group is currently the most recent form of ACE inhibitor items developed and that this is a combination of two different drugs (an ACE inhibitor and another drug) in one product.

Categories (D and A) ACE inhibitor items have the highest average cost of all ACE inhibitor items in the database this could be due to their higher frequencies (23 272 and 39 522) when compared to the frequency of categories (B and C) ACE inhibitor items (4 486 and 882), which have substantially lower average costs.

Table 5.6 Effect sizes (d-values) of the costs of ACE inhibitor items according to the chemical category classification.

Chemical Category Classification	Category A	Category B	Category C	Category D
Category A		0.63	0.22	0.50
Category B	0.63		0.48	1.00
Category C	0.22	0.47		0.86
Category D	0.50	1.00	0.86	

*For the purpose of this study effect sizes (d-values) of 0.8 or higher will be assumed to have practical significance (refer to paragraph 4.6.4).

Table 5.6 represents the effect sizes (d-values) of the average medicine costs of ACE inhibitor items according to the chemical category classification. For the purpose of this study, effect sizes (d-values) of 0.8 or higher will be assumed to have practical significance with the shaded area indicating the instances where practical significant differences occur. The d-value of 0.86 and 1.00, derived from the average medicine costs of categories (C and D) and also from categories (B and D) respectively, is an indication of the only practical significant difference between the average costs of these individual categories.

The rest of the categories have a d-value of less than 0.8, thus it can be concluded that there is no practical significant difference between the average medicine costs of categories A and B, neither between categories A and C. There is also no practical significant difference between categories A and D, neither between categories B and C.

In conclusion, category D shows to be the category with the most cost implication of all the categories.

5.4.2. Cost analysis of ACE inhibitor items according to the twenty active ingredient (typical product item) classification.

Table 5.7 Cost analysis of ACE inhibitor items according to the twenty active ingredient classification.

Active ingredients (typical product item)	Number of ACE inhibitors	Average cost (R)	Standard deviation (R)	Min. Cost (R)	Max. Cost (R)
1. Enalapril	8635	196.65	85.55	0.79	662.28
2. Lisinopril	7784	146.06	66.44	0.74	556.91
3. Cilazapril	551	156.72	42.89	49.25	295.06
4. Perindopril	10297	213.39	54.27	1.07	652.15
5. Quinalapril	3382	170.31	54.14	1.57	840.99
6. Ramipril	7997	221.40	73.88	1.14	489.57
7. Benazepril	139	169.78	53.64	30.24	264.37
8.Trandolapril	737	296.10	106.88	2.72	814.59
9.Captopril	4486	129.84	102.64	0.33	654.34
10.Fosenopril	882	178.59	46.69	57.68	436.32
11.Benazepril + HCTZ	92	236.66	42.26	116.67	264.46
12. Trandolapril + verapamil HCl	1508	306.97	55.13	110.85	597.50
13. Fosenopril + HCTZ	398	217.63	22.49	121.20	501.46
14. Captopril + HCTZ	1104	178.25	55.36	1.56	484.86
15. Quinalapril + HCTZ	6040	188.33	42.22	0.81	470.52
16. Perindopril + indapamide	1622	234.11	45.02	2.44	487.84
17. Cilazapril + HCTZ	404	200.67	25.82	2.62	264.25
18. Lisinopril + HCTZ	5642	234.84	58.57	13.89	556.87
19. Enalapril + HCTZ	4779	275.50	44.63	0.31	608.55
20. Ramipril + felodipine	1683	243.64	65.28	1.86	589.34

Table 5.7 provides the data of the cost analysis of ACE inhibitor items, according to the twenty active ingredients.

In order to ensure a clearer picture of the main contributors to the total average cost of ACE inhibitor items present on the medicine claims database, the active ingredients with an average cost of R200.00 and more are analysed and summarised in table 5.8. Of the twenty active ingredients, eleven have an average cost greater than R200.00.

Table 5.8 The average costs (R) of the active ingredients exceeding R200 as well as the standard deviations (R).

Active ingredients	Average cost (R)	Standard deviation (R)
4. Perindopril	213.39	54.27
6. Ramipril	221.40	73.88
8.Trandolapril	296.10	106.87
11.Benazepril + hydrochlorothiazide	236.66	42.26
12. Trandolapril + verapamil HCl	306.97	55.13
13. Fosenopril + HCTZ	217.63	22.49
16. Perindopril + indapamide	234.11	45.02
17. Cilazapril + HCTZ	200.67	25.82
18. Lisinopril + HCTZ	234.84	58.57
19. Enalapril + HCTZ	275.50	44.63
20. Ramipril + felodipine	243.64	65.28

More than half of the ACE inhibitor items which were analysed had an average cost of greater than R200.00 thus contributing to the high average cost of ACE inhibitor items. It can thus be concluded that active ingredients: (Trandolapril + Verapamil hydrochloride) and Trandolapril are the two active ingredients that have the largest average costs. One of the contributing factors to these high average costs may be that they are both original drugs.

According to table 5.9, which depicts the effect sizes (d-values) of the ACE inhibitor items according to the active ingredient classification (with the shaded area indicating the instances where practical significant differences occur), a vast majority of ACE inhibitors have d-values larger than 0.8 and this is an indication of a number of instances where practical significant differences between the average costs of the compared active ingredients exist.

Table 5.9 Effect sizes (d-values) of the costs of ACE inhibitor items according to the twenty active ingredient (AI) classification.

AI	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	x																			
2	0.59	x																		
3	0.46	0.16	x																	
4	0.19	1.01	1.04	x																
5	0.30	0.36	0.25	0.79	x															
6	0.28	1.01	0.87	0.10	0.69	x														
7	0.31	0.35	0.24	0.80	0.00	0.70	x													
8	0.93	1.40	1.30	0.77	1.17	0.70	1.18	x												
9	0.65	0.15	0.26	0.81	0.39	0.89	0.39	1.55	x											
10	0.21	0.49	0.47	0.64	0.15	0.58	0.16	1.10	0.47	x										
11	0.46	1.36	1.86	0.42	1.22	0.20	1.25	0.55	1.04	1.24	x									
12	1.29	2.42	2.72	1.70	2.47	1.16	2.49	0.10	1.72	2.33	1.27	x								
13	0.24	1.07	1.42	0.07	0.87	0.05	0.89	0.73	0.85	0.84	0.45	1.62	x							
14	0.21	0.48	0.38	0.63	0.14	0.58	0.15	1.10	0.47	0.00	1.05	2.32	0.71	x						
15	0.09	0.63	0.74	0.46	0.33	0.45	0.34	1.00	0.56	0.21	1.14	2.15	0.69	0.18	x					
16	0.44	1.33	1.72	0.38	1.18	0.17	1.19	0.58	1.01	1.19	0.05	1.32	0.36	1.00	1.02	x				
17	0.04	0.82	1.02	0.23	0.56	0.28	0.57	0.89	0.69	0.47	0.85	1.92	0.65	0.40	0.29	0.74	x			
18	0.45	1.33	1.33	0.36	1.10	0.18	1.11	0.57	1.02	0.96	0.03	1.23	0.29	0.96	0.79	0.01	0.58	x		
19	0.92	1.94	2.66	1.14	1.94	0.73	1.97	0.19	1.42	2.08	0.87	0.57	1.30	1.76	1.95	0.93	1.68	0.69	x	
20	0.55	1.47	1.33	0.46	1.12	0.30	1.13	0.49	1.11	0.99	0.11	0.98	0.40	1.00	0.85	0.14	0.66	0.13	0.49	x

AI = Active ingredient

The active ingredients in Table 5.9 are represented according to the numerical values as in Table 5.1.

5.5. ANALYSIS OF ACE INHIBITOR ITEMS ACCORDING TO THE INNOVATOR/GENERIC CLASSIFICATION OF ACE INHIBITORS

5.5.1. Prevalence and cost of ACE inhibitor items according to the innovator/generic classification of ACE inhibitors.

As qouted by Joubert (2002:210), "Herbert & Roche stipulated that an increase in the number of prescriptions written, the use of more expensive drugs and price increases are all factors that contribute to the high cost of medicine. Mehl and Santell state that the generic drug industry has been expanding and sales of generics are expected to increase to 20 billion United States dollars by the year 2005. In support of this view, Pearson adds that generics account for approximately 50% of all drugs dispensed in primary care, in the United States of America. However, as mentioned previously, there is still a tendency of prescribing the more expensive innovator form of ACE inhibitor items as first-line therapy".

An analysis of the prevalence, cost and cost index values of ACE inhibitor items based on the innovator/generic classification of ACE inhibitors will follow. All the ACE inhibitor items that were available on the database at the time of the study will be included in the analysis that follows and are classified as innovator or generic ACE inhibitors. This classification of ACE inhibitor items, as innovator or generic agents, is based on the following criteria, which was set specifically for this study:

- The dosage indications for both the innovator and its generic counterpart must be identical.
- Both the innovator and generic agents must contain the same active ingredient.

In the research, ACE inhibitors will be classified as innovator or generic agents according to the active ingredient and the dosage indications as quoted by Snyman (2002: 135).

Table 5.10. Pervalence, cost and cost index values of ACE inhibitor items based on the innovator/ generic classification.

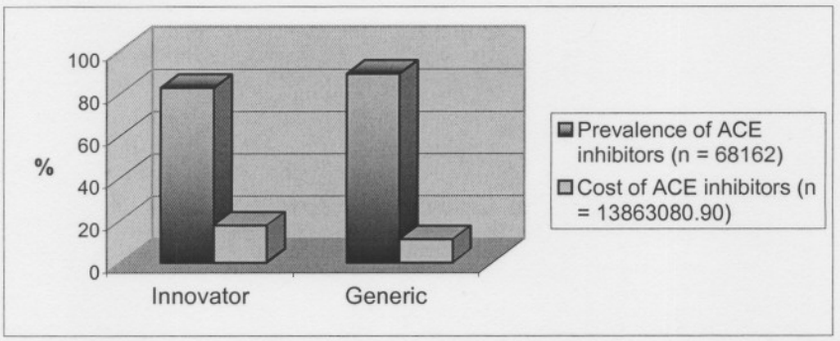
Innovator or Generic	Prevalence of ACE inhibitors	Prevalence of ACE inhibitors (n=68 162) (%)	Cost of ACE inhibitors (R)	Cost of ACE inhibitors (n=R13 863 080.90) (%)	Cost index
Innovator	56 278	82.57	12 353 244.93	89.11	1.08
Generic	11 884	17.44	1 509 835.97	10.89	0.62
Total	68 162	100	13 863 080.90	100	-

Table 5.10 indicates that, of the 68 162 ACE inhibitor items available on the database 56 278 are classified as innovator ACE inhibitors, at a cost of R12 353 244.93, while the remaining 11 884 ACE inhibitor items constitute the generic ACE inhibitors, with a cost of R1 509 835.97.

Figure 5.4 is an illustration of the prevalence and cost percentages of the innovator and generic ACE inhibitors. From this figure, it is clear that the innovator ACE inhibitors have a higher prevalence percentage (82.57%; n =68 162) than the prevalence percentage of the generic ACE inhibitors (17.44%; n =68 162). A possible explanation for the higher prevalence of the innovator drugs may be attributed to the myth, believed by a substantial number of the general public, that the use of generic medications has some sort of risk associated with it and they are not as effective as their innovator equivalents. But from the analysis the other contributing factor may be that not all ACE inhibitors have generic alternatives.

In a recent survey conducted by Merck-Medco (as qouted by Joubert, 2002: 211), the percentage of patients who believed that generic drugs were riskier than the innovator drugs varied from 14.2% to 53.8% and that the perceived risk of generic versus innovator drugs varied with the condition being treated. One of the regulations set for generics is that there may be no evidence to suggest that the utilisation of generic alternative products will impair the outcome of the care provided.

Figure 5.4 Prevalence and cost percentages of ACE inhibitor items based on the innovator/generic classification.



The cost percentages between the innovator and generic ACE inhibitors differ considerably. The cost percentage of the innovator ACE inhibitors is (89.11%; n =R13 863 080.90) and the cost percentage of the generic ACE inhibitors is (10.89%; n =R13 863 080.90). This gives a difference of 78.22% between innovator ACE inhibitors (89.11%) and generic ACE inhibitors (10.89%), thus emphasising the high costs associated with the innovator ACE inhibitors.

Figure 5.5 Cost index values of ACE inhibitor items based on the innovator/generic classification.

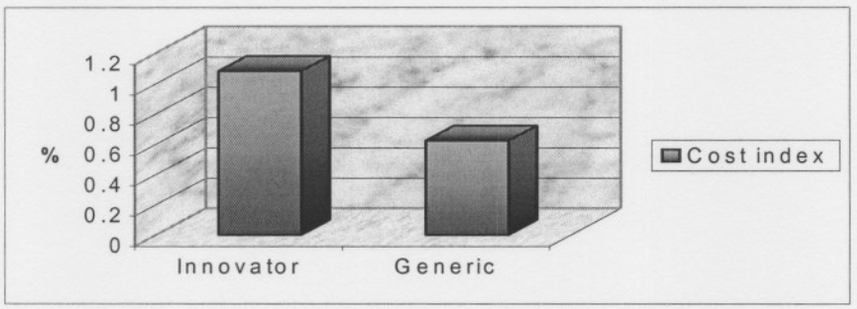


Figure 5.5 is an illustration of the cost index values of the innovator and generic ACE inhibitor items, a cost index value exceeding one for the innovator ACE inhibitors is understandable due to the high cost associated with it as said above (refer to table 5.10).

The innovator ACE inhibitors have a relatively high cost in comparison with their prevalences.

5.5.2. Prevalence and cost of ACE inhibitor items according to the four-fold classification of ACE inhibitors.

Table 5.11 is a summary of the prevalence, cost and cost index values of the innovator and generic ACE inhibitor items according to the four-fold classification of ACE inhibitors (refer to paragraph 5.3) used throughout this study, though in this specific analysis (5.5.2) the dosage quantities will not be analysed as yet.

Table 5.11 Prevalence, cost and cost index values of innovator/generic ACE inhibitor items.

Innovator/ Generic	Chemical category classification	Active ingredient (typical product item) classification	Frequency of ACE inhibitor items	Prevalence of ACE inhibitor items (n=68 162) (%)	Cost of ACE inhibitor items (R)	Cost of ACE inhibitor items (n=R1386 3080.90) (%)	Cost index
Innovator	Category A	Enalapril	6 523	9.57	1 344 156.89	9.70	1.01
		Lisinopril	2 811	4.12	532 697.94	3.84	0.93
		Cilazapril	551	0.81	86 356.37	0.62	0.76
		Perindopril	10 297	15.11	2 197 237.70	15.85	1.05
		Quinalapril	3 382	4.96	575 995.37	4.15	0.84
		Ramipril	7 997	11.73	1 770 577.53	12.77	1.09
		Benazapril	139	0.20	23 600.05	0.17	0.85
		Trandolapril	737	1.08	218 227.11	1.57	1.45
	Category B	Captopril	1000	1.47	256 093.27	1.85	1.26
	Category C	Fosenopril	882	1.29	157 519.93	1.14	0.88
	Category D	Benazapril +	92	0.13	21 772.63	0.16	1.23
		Trandolapril +	1 508	2.21	462 908.28	3.34	1.51
		Fosenopril +	398	0.57	84 657.48	0.61	1.07
		Captopril +	288	0.42	68 574.19	0.49	1.17
		Quinalapril +	6 040	8.86	1 137 499.12	8.21	0.93
		Perindopril +	1 622	2.38	379 720.97	2.74	1.15
		Cilazapril +	404	0.59	81 070.16	0.58	0.98
		Lisinopril +	5 642	8.28	1 324 955.26	9.56	1.15
		Enalapril +	4 282	6.28	1 219 577.08	8.80	1.40
		Ramipril +	1 683	2.47	410 047.60	2.96	1.20
Generic	Category A	Enalapril	2 112	3.10	353 961.41	2.55	0.82
		Lisinopril	4 973	7.30	604 246.13	4.36	0.60
	Category B	Captopril	3 486	5.11	326 390.41	2.35	0.46
	Category C	absent	-	-	-	-	-
	Category D	Captopril +	816	1.20	128 218.82	0.92	0.77
		Enalapril +	497	0.73	97 019.20	0.70	0.96
TOTAL			68 162	99.97	13863 080.90	99.63	

*The sum of the percentage columns does not amount to 100 due to the fact that amounts were rounded off to two decimals.

5.6 COST ANALYSIS OF ACE INHIBITORS ACCORDING TO THE INNOVATOR/GENERIC CLASSIFICATION OF ACE INHIBITORS

According to Mehl and Santell (quoted by Joubert, 2002: 217), the generic drug industry is an important factor in the usage, pricing and cost of drugs. However, the need for affordable and accessible drugs must not be overshadowed by the development of an exciting and expanding drug industry (the innovator drugs).

A cost analysis of the innovator and generic ACE inhibitor items will follow in an attempt to indicate the cost differences that exist between the innovator and generic ACE inhibitors. Note, however, that the effect size (d-value) of 0.8 or higher will be assumed to have practical significance. As thus the innovator and generic ACE inhibitors have a d-value of 1.28 indicating that there is a practical significant difference between the average cost of the innovator and the generic ACE inhibitors (refer to table 5.12).

From the cost analysis conducted for the total number of innovator and generic ACE inhibitor items, depicted in table 5.12, it can be concluded that the innovator ACE inhibitors have the highest average cost (R219.54 ± R72.11) as well as the highest maximum cost (R840.99) when compared to the generic ACE inhibitors that have an average cost of R127.05 ± R59.06 and a maximum cost of R427.27. The difference between the average and maximum costs of the two separate groups is also an indication of the high costs that are associated with innovator ACE inhibitors.

Table 5.12 Cost analysis of ACE inhibitor items according to the innovator/generic classification.

ACE inhibitors innovator/ generic	Number of ACE inhibitors	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)	Effect size (d-value)
Innovator	**56278**	**219.54**	**72.11**	**0.81**	**840.99**	**1.28**
Generic	**11884**	**127.05**	**59.06**	**0.31**	**427.27**	

*For the purpose of this study effect sizes (d-values) of 0.8 or higher will be assumed to have practical significance

It was thus found that if a hundred percent of all the prescriptions for ACE inhibitor items could be generically substituted, R5 203 098.00, over a twelve-month period could be saved. This was found by taking the total cost of all ACE inhibitor items in the database, i.e. R13 863 080.90, minus the product of the average cost of each individual generic ACE inhibitor (R1 509 835.97/11 884= R127.05) and the total ACE inhibitor items in the database, i.e. 68 162. This can be given by R13 863 080.90 - (127.05 X 68 162)= R5 203 098.00.

However, the fact that not all the innovator ACE inhibitors have generic equivalents available must be taken into account. 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. This was found by adding all the costs saved by substituting innovator drugs with thier generics.

A comparative analysis of the prevalence and costs as well as a cost analysis of the individual innovators and their particular generic forms will follow in paragraph 5.7.

5.7 A COMPARATIVE ANALYSIS OF THE PREVALENCE AND COST OF INNOVATOR AND GENERIC ACE INHIBITOR ITEMS

The following is an analysis of the usage and costs of innovator ACE inhibitors in comparison with their equivalent generic forms, this analysis is to indicate the precise innovator/generic usage and the effect that the usage has on the costs of ACE inhibitor items.

Table 5.13 is a summary of the ACE inhibitor items that are not included in this analysis since they are the innovator ACE inhibitors that do not have any generic equivalents available at the time of analysis.

Table 5.13 Innovator ACE inhibitor items excluded from the comparative analysis.

Innovators excluded:	
Prinzide®	Cibadrex®
Zestril®	Tarka®
Inhibace®	Monozide®
Coversyl®	Accuretic®
Accupril®	Coversyl plus®
Ramace®	Inhibace plus®
Tritace®	Zestoretic®
Cibace®	Tri-plen®
Gopten®	Tri-plen forte®
Monopri®l	
Renitec® 2.5mg	
Captoretic HS®	

In order to give structure to the analysis of the innovator drugs and their equivalent generic forms they will be analysed according to their active ingredients. However, it is important to note that not all the active ingredient-forms of ACE inhibitor items (as used earlier in the study) will be utilised due to the fact that certain ACE inhibitor items were absent in the database and some of them did not have the generic equivalents at the time of the analysis (refer to table 5.13).

It is important to note that the prevalence and cost percentages will be calculated using the total number of ACE inhibitor items available on the database (n =68 162) and the total cost of the ACE inhibitor items on the medical claims database (n =R13 863 080.90) during the study period. Thus, the prevalence and cost percentages used throughout the comparative analysis are representative for the total number of ACE inhibitor items and the total cost of ACE inhibitor items on the overall database.

5.7.1. Enalapril: innovator/generic analysis

5.7.1.1. Renitec® 5 mg

Table 5.14 Prevalence, cost and cost index values of Renitec® 5mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Renitec® 5mg Tab		1 366	2.00	177 616.99	1.28	0.64
	Adco-Enalapril® 5mg Tab.	11	0.02	1 056.67	0.01	0.50
	Alapren® 5mg Tab.	25	0.04	2 388.37	0.02	0.50
	Enap® 5mg Tab.	10	0.015	710.46	0.005	0.34
	Hypace® 5mg Tab.	38	0.06	1829.64	0.65	1.03
Total innovator		1366	2.00	177 616.99	1.28	-
Total generic		84	0.12	5 985.14	0.04	-

*Note that for Enap® Tablets, the values are given in three decimals to avoid confusion since the values are too small.

In paragraph 5.5.1 it was stated that there is a tendency in prescribing the more expensive innovator form of ACE inhibitors as first-line therapy. This statement can be supported by the data depicted in table 5.14, where Renitec® 5mg Tab. (innovator drug) has the highest prevalence (2.00%; n =68 162) with a cost representing 1.28% (n =R13 863 080.90) in comparison with its generic equivalents, where none of them has a prevalence or cost percentage greater than 1 in the overall data. However, both the innovator and the generic items have a cost index value less than 1, thus indicating that Renitec® 5mg Tab. and its generics are not too expensive.

Table 5.15 Cost analysis of Renitec® 5mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Total (R)
Renitec® 5mg Tab.		1366	130.03	39.25	177 616.99
	Adco-Enalapril® 5mg Tab.	11	96.06	3.40	1 056.67
	Alapren® 5mg Tab.	25	95.53	2.22	2 388.37
	Enap® 5mg Tab.	10	71.05	2.27	710.46
	Hypace® 5mg Tab.	38	48.15	36.14	1829.70

Table 5.15 is a cost analysis of Renitec® 5mg tablets and its equivalent generic forms. Renitec® 5mg has the highest average cost (R130.03± R39.25). Adco-Enalapril® 5mg Tab. and Alapren® 5mg Tab. have the higher average cost (R96.06 ± R3.40) and (R95.53 ± 2.22) respectively of all the generic equivalents. Hypace® 5mg Tab. has the lowest average cost (R48.15± R36.14). Although Hypace® 5mg Tab. has a low average cost, Enap® 5mg Tab. is still the least prescribed as seen in table 5.15. Renitec® 5mg Tab also has the highest total cost (R177 616.99) in comparison with its generic forms but it is still the most popular drug in the group.

It was found that if all the prescriptions containing Enalapril® 5mg Tab. were generically substituted, R80 289.63, could be saved. The amount was derived from the following calculation: The total cost of all the Enalapril 5mg Tab. (innovator and generics) (R183 602.13) minus the product of the usage cost per generic Enalapril 5mg Tab. items
(R5 985.14/84=R71.25) and the total number of Enalapril 5mg Tab. items prescribed (1366+84=1450). Thus R183 602.13– (71.25 x 1450) = R80 289.63.

5.7.1.2. Renitec® 10mg tab.

Table 5.16 Prevalence, cost and cost index values of Renitec® 10mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Renitec® 10mg Tab.		2462	3.61	426 192.44	3.07	0.85
	Adco-Enalapril® 10mg Tab.	31	0.05	3 884.90	0.03	0.60
	Alapren® 10mg Tab.	37	0.05	4 003.82	0.03	0.60
	Enap® 10mg Tab.	10	0.02	1 233.24	0.010	0.50
	Pharmapress® 10mg Tab.	1041	1.53	138 286.59	1.00	0.65
Total innovator		2462	3.61	426 192.44	3.07	-
Total generic		1119	1.64	147 408.55	1.06	-

It can be derived from table 5.16 that Renitec® 10mg Tab. which is an innovator drug has the highest prevalence (3.61%; n =68162) and cost (3.07%; n =R13863080.90). Pharmapress® 10mg Tab has shown to have at least a greater prevalence (1.53%; n =68162) and cost (1.00%; n = R13863080.90) as compared to the other generic products in this group which are almost non-existant. The calculated cost index values, for Renitec® 10mg Tab. and its alternative generics are all below one, thus indicating a slightly higher prevalence in comparison to the costs of these drugs, which implies that they are not very expensive.

Table 5.17 Cost analysis of Renitec® 10mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	maximum cost of ACE inhibitors (R)
Renitec® 10mg Tab.		2462	173.11	57.23	526.98
	Adco-Enalapril® 10mg Tab.	31	125.32	33.69	232.84
	Alapren® 10mg Tab.	37	108.21	20.34	122.05
	Enap® 10mg Tab.	10	123.32	47.18	201.14
	Pharmapress® 10mg Tab.	1041	132.84	44.67	393.74

From the cost analysis of these agents it is evident that Renitec® 10mg Tab. has the highest average cost (R173.11± R57.23), followed by Pharmapress® 10mg Tab (R132.84± R44.67). Alapren® 10mg Tab. has the lowest average cost (R108.21± R20.34). However, it is clear that the innovator form (Renitec® 10mg Tab.) has the highest maximum cost (R526.98) followed by Pharmapress® 10mg Tab. (R393.74). Though these drugs have this high average and total cost, they are the most prescribed (refer to table 5.17).

It was found that if all the prescriptions containing Enalapril® 10mg Tab. were generically substituted, R101 875.86, could be saved. The amount was derived from the following calculation: The total cost of all the Enalapril 10mg Tab. (innovator and generics) (R573 600.99) minus the product of the usage cost per generic Enalapril 10mg Tab. items (R147 408.55/1119=R131.73) and the total number of Enalapril 10mg Tab. items prescribed (2462+1119=3581). Thus R573 600.99– (131.73 x 3581) = R101 875.86.

5.7.1.3. Renitec® 20mg tab.

Table 5.18 Prevalence, cost and cost index values of Renitec® 20mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 153) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Renitec® 20mg Tab.		2459	3.61	719 760.95	5.19	1.44
	Adco-Enalapril® 20mg Tab.	27	0.04	5 495.07	0.04	1.00
	Alapren® 20mg Tab.	16	0.02	3 095.72	0.02	1.00
	Enap® 20mg Tab.	8	0.012	1 788.11	0.01	1.08
	Pharmapress® 20mg Tab.	896	1.31	192 018.46	1.39	1.06
Total innovator		2459	3.61	719 760.95	0.05	-
Total generic		947	1.39	202 397.36	1.46	-

From the data depicted in table 5.18 that Renitec® 20mg Tab. has the highest prevalence (3.61%; n =68162) and cost (5.19%; n =R13 863 080.90) in comparison with its generic equivalents. It is important to note, too, that all agents depicted in table 5.18 have cost index values equal to or exceeding one, thus all these drugs have a relatively high cost in comparison to their particular prevalences.

Table 5.19 Cost analysis of Renitec® 20mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	maximum Cost (R)
Renitec® 20mg Tab.		2459	292.71	59.50	610.93
	Adco-Enalapril® 20mg Tab.	27	203.52	65.55	384.81
	Alapren® 20mg Tab.	16	193.48	51.55	386.33
	Enap® 20mg Tab.	8	223.51	79.01	297.42
	Pharmapress® 20mg Tab.	896	214.31	60.94	421.98

From the cost analysis of these agents it is evident that Renitec® 20mg Tab. has the highest average cost (R292.70± R59.50), followed by Enap® 20mg Tab. (R223.51± R79.01) and then Pharmapress® 20mg Tab. with an average cost of R214± R60.94. However, it is clear that the innovator form (Renitec® 20mg Tab.) has the highest maximum cost (R610.93) followed by Pharmapress® 20mg Tab. (R421.98). Thou Enap® 20mg Tab. has the second high average cost, its maximum cost is the lowest (R297.42), and this could be because it has the lowest prevalence value of the whole group (refer to table 5.19).

It was found that if all the prescriptions containing Enalapril® 20mg Tab. were generically substituted, R194 227.99, could be saved. The amount was derived from the following calculation: The total cost of all the Enalapril 20mg Tab. (innovator and generics) (R922 158.31) minus the product of the usage cost per generic Enalapril 20mg Tab. items (R202 397.36/947=R213.72) and the total number of Enalapril 20mg Tab. items prescribed (2459+947=3406). Thus R922 158.31– (213.72 x 3406) = R194 227.99.

5.7.2. Lisinopril: innovator/generic analysis

5.7.2.1. Prinivil® 5mg tab.

Table 5.20 Prevalence, cost and cost index values of Prinivil® 5mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Prinivil® 5mg Tab.		21	0.03	2 898.84	0.02	0.67
	Zestomax® 5mg Tab.	871	1.28	55 177.47	0.40	0.3
Total innovator		21	0.03	2 898.84	0.02	-
Total generics		871	1.28	55 177.47	0.40	-

Table 5.20 represents the prevalence, cost, prevalence and cost percentages and the cost index values of Prinivil ® 5mg Tab. and its associated generic. Zestomax® 5mg Tab. (a generic of Prinivil ® 5mg Tab.) has the highest prevalence (1.28%; n =68 162). The cost index values of both agents are not more than 1, thus the cost is less than the prevalence, which implies that the cost is relatively low.

Table 5.21 Cost analysis of Prinivil ® 5mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Prinivil® 5mg Tab.		21	138.04	0	138.04	138.04
	Zestomax® 5mg Tab.	871	63.35	31.37	0.74	160.52

The higher prevalence of Zestomax® 5mg Tab. can be seen as positive utilisation of the generic forms of ACE inhibitors, due to the fact that Zestomax® 5mg Tab. has the prevalence percentage of 1.28 compared to its innovator form Prinivil® 5mg Tab. with the prevalence percentage of 0.03 (refer to table 5.20).

5.7.2.2 Prinivil® 10mg tab.

Table 5.22 Prevalence, cost and cost index values of Prinivil® 10mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence of ACE inhibitors	Prevalence of ACE inhibitors (n=68 162) (%)	Cost of ACE inhibitors (R)	Cost of ACE inhibitors(n =R13 863 080.90) (%)	Cost index
Prinivil® 10mg Tab.		26	0.04	4 511.11	0.03	0.75
	Zestomax® 10mg Tab.	2160	3.17	223 513.14	1.61	0.51
Total innovator		26	0.04	4 511.11	0.03	0.75
Total generics		2160	3.17	223 513.14	1.61	0.51

Table 5.22 represents the prevalence, cost prevalence and cost percentages and the cost index values of Prinivil ® 10mg Tab. and its associated generic. Zestomax® 10mg Tab. which has the highest prevalence (3.17%; n =68 162) whereas the innovator agent Prinivil ® 10mg Tab has the prevalence of (0.04%; n =68 162). The cost index values of both agents are not more than 1, thus the cost is less than the prevalence indicating that the cost of the drug is relatively low.

Table 5.23 Cost analysis of Prinivil ® 10mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Prinivil® 10mg Tab.		26	173.50	38.23	101.48	193.99
	Zestomax® 10mg Tab.	2160	103.48	14.68	27.42	220.38

The higher prevalence of Zestomax® 10mg Tab. can be seen as positive utilisation of the generic forms of ACE inhibitors, due to the fact that the average cost (R103.48 ± R14.68) is lower than that of the innovator agent Prinivil ® 10mg Tab. (R173.50 ± R38.23). The maximum cost of Zestomax® 10mg Tab. (R220.38) is higher than that

of Prinivil ® 10mg Tab. (R193.99), this could be due to the high prevalence of Zestomax® 10mg Tab. (Refer to table 5.23).

5.7.2.3. Prinivil® 20mg tab.

Table 5.24 Prevalence, cost and cost index values of Prinivil® 20mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Prinivil® 20mg Tab.		39	0.06	12 421.75	0.09	1.50
	Zestomax® 20mg Tab.	1942	2.85	325 555.52	2.35	0.82
Total innovator		39	0.06	12 421.75	0.09	-
Total generics		1942	2.85	325 555.52	2.35	-

Table 5.24 represents the prevalence, cost, prevalence and cost percentages and the cost index values of Prinivil ® 20mg Tab. and its generic Zestomax® 20mg Tab, Zestomax® 20mg Tab. has the highest prevalence (2.85%; n =68 162). The cost index value of Zestomax® 20mg Tab. is less than 1 thus the cost is not greater than the prevalence whereas the cost index value of Prinivil ® 20mg Tab. is greater than one indicating that its cost is greater than its prevalence, thus the cost of the drug is relatively high.

Table 5.25 Cost analysis of Prinivil® 20mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Prinivil ® 20mg Tab.		39	318.51	37.73	161.48	347.82
	Zestomax® 20mg Tab.	1942	167.64	28.31	31.58	351.38

The higher prevalence of Zestomax® 20mg Tab. can be seen as positive utilisation of the generic forms of ACE inhibitors, which might be asscribed to the fact that the

average cost of Zestomax® 20mg Tab. (R167.64± R28.31) is much less than that of Prinivil ® 20mg Tab. (R318.51± R37.73). The maximum cost of Zestomax® 20mg Tab. (R351.38) may be higher compared to that of Prinivil ® 20mg Tab., this may be due to the fact that Zestomax® 20mg Tab. has a much higher prevalence percentage of 2.85 than Prinivil ® 20mg Tab. with the prevalence percentage of 0.06 (Refer to table 5.24).

5.7.3. Captopril: innovator/generic analysis

5.7.3.1. Capoten hs® 12.5mg Tab.

Table 5.26 Prevalence, cost and cost index values of Capoten HS® 12.5mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Capoten HS® 12.5mg		134	0.20	22 190.34	0.16	0.80
	CaptoHexal® 12.5mg Tab.	164	0.24	14 211.64	0.10	0.42
	Captopril-acet® 12.5mg Tab	9	0.01	571.38	0.004	0.40
	CardiACE® 12.5mg Tab	2	0.002	151.43	0.001	0.50
Total innovator		134	0.20	22 190.34	0.16	-
Total generic		175	0.26	14 934.45	0.11	-

When analysing the data that were obtained from the medicine claims database it was found that all the agents (innovator and generics) have cost index values of less than 1, thus all drugs constitute relatively low costs in comparison to their specific prevalences (refer to table 5.26).

Table 5.27 Cost analysis of Capoten HS® 12.5mg Tab. and its equivalent generic.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Capoten HS® 12.5mg		134	165.60	74.86	3.36	259.91
	CaptoHexal® 12.5mg Tab.	164	86.66	33.33	18.44	184.55
	Captopril-acet® 12.5mg Tab.	9	63.49	22.21	51.44	102.51
	CardiACE® 12.5mg Tab.	2	75.72	34.77	51.13	100.30

CardiACE® 12.5mg Tab. has the lowest prevalence percentage of 0.002% and yet with a low average cost (R75.72 ± R34.77) and the lowest maximum cost (R100.30) whereas the most popular drug in terms of prevalence is CaptoHexal® 12.5mg Tab. with a prevalence percentage of 0.24% and a relatively high average cost (R86.6 ± R33.33) and a high maximum cost (R184.55). Thou CaptoHexal® 12.5mg Tab. has a high prevalence percentage (0.24) and relativelly high cost, its innovator has the second highest prevalence (n=134) to it and with the highest average cost of (R165.60± R74.86) and a maximum cost of R259.91.

It was found that if all the prescriptions containing Captopril® 12.5mg were generically substituted, R26 369.97, could be saved. The amount was derived from the following calculation: The total cost of all the Captopril 12.5 mg Tab. (innovator and generics) (R37 124.79) minus the product of the usage cost per generic Captopril 12.5mg Tab. items (R14 934.45/175=R85.34) and the total number of Captopril 12.5mg Tab. items prescribed (134+175=309). Thus R37 124.79– (85.34x 309) = R26 369.97

5.7.3.2 Capoten® 25mg Tab.

Table 5.28 Prevalence, cost and cost index values of Capoten® 25mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Capoten® 25mg Tab.		501	0.74	98 580.50	0.71	0.96
	Adco-Captopril® 25mg Tab.	378	0.55	26 941.22	0.19	0.35
	Apo-Captopril® 25mg Tab.	13	0.02	1 026.86	0.01	0.50
	Capace® 25mg Tab.	810	1.19	70 827.02	0.51	0.43
	CaptoHexal® 25mg Tab.	44	0.06	4 864.94	0.04	0.67
	Captomax® 25mg Tab.	827	1.21	62 066.94	0.45	0.37
	Captopril-acet® 25mg Tab.	24	0.04	1 989.73	0.01	0.25
	CardiACE® 25mg Tab.	26	0.04	2 253.32	0.02	0.50
	Merck-Captopril® 25mg Tab.	4	0.01	266.31	0.001	0.10
	Rolab-Captopril® 25mg Tab.	210	0.31	15 137.42	0.11	0.35
	Zapto ® 25mg Tab.	202	0.30	15 553.07	0.11	0.37
Total innovator		501	0.73	98 580.50	0.71	-
Total generic		2538	3.72	200 926.83	1.45	-

According to the classification of ACE inhibitors as innovator/generic drugs, Capoten® 25mg Tab. was identified as an innovator ACE inhibitor, with 10 alternative generic equivalents (Summarised in table 5.28). However, even with the large number of equivalents of Capoten® 25mg Tab. available, Captomax® 25mg Tab. and Capace® 25mg Tab. have the highest prevalence (1.21%; n=68162) and cost (0.45%; n=R13 863 080.90), (1.19%; n=68162) and cost (0.51%; n=R13 863 080.90) respectively. All

the agents in this group have cost index values that are lower than 1 thus indicating that these agents constitute relatively low costs in comparison to their specific prevalences.

Table 5.29 Cost analysis of Capoten ® 25mg Tab.and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Capoten® 25mg Tab.		501	196.77	90.68	0.84	654.34
	Adco-Captopril® 25mg Tab.	378	71.27	28.37	11.57	226.91
	Apo-Captopril® 25mg Tab.	13	78.99	31.49	49.80	136.80
	Capace® 25mg Tab.	810	87.44	41.62	0.84	262.94
	CaptoHexal® 25mg Tab.	44	110.57	53.17	0.33	206.45
	Captomax® 25mg Tab.	827	75.05	32.80	0.84	261.47
	Captopril-acet® 25mg Tab.	24	82.91	13.17	74.73	129.64
	CardiACE® 25mg Tab.	26	86.67	7.56	49.59	88.69
	Merck-Captopril® 25mg Tab.	4	66.58	43.82	0.84	88.50
	Rolab-Captopril® 25mg Tab.	210	72.08	28.90	0.70	136.80
	Zapto ® 25mg Tab.	202	77.00	27.62	33.69	175.95

A cost analysis of Capoten® 25mg Tab. and its alternative generic forms (depicted in table 5.29) indicates that Capoten® 25mg Tab. has the highest average cost (R196.77± R90.68) and maximum cost (R654.34) when compared to the average and maximum costs of its generics. It is the 3rd most popular agent of the group with the prevalence percentage of 0.74 whereas Captomax® 25mg Tab. is the most popular with the prevalence percentage of 1.21 with the average cost (R75.05 ± R32.80) followed by

Capace® 25mg Tab.with the prevalence percentage of 1.19 and an average cost of (R87.44 ± R41.62), both have an average maximum cost of R261.47 and R262.94 respectively. Of the entire group, Merck-Captopril® 25mg Tab. has the lowest average cost (R66.58 ± R43.82) and the maximum cost of R88.50 and yet it is the least prescribed with the prevalence percentage of only 0.01.

It was found that if all the prescriptions containing Captopril® 25mg Tab. were generically substituted, R58 909.70, could be saved. The amount was derived from the following calculation: The total cost of all the Captopril 25mg Tab. (innovator and generics) (R299 507.33) minus the product of the usage cost per generic Captopril® 25mg Tab. items (R200 926.83/2538=R79.17) and the total number of Captopril 25mg Tab. items prescribed (501+2538=3039). Thus R299 507.33– (79.17 x 3039) = R58 909.70

5.7.3.3. Capoten® 50mg tab.

Table 5.30 Prevalence, cost and cost index values of Capoten® 50mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Total Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Capoten® 50mg Tab.		365	0.54	135 322.43	0.98	1.85
	Adco-Captopril® 50mg Tab.	177	0.26	25 119.33	0.18	0.69
	Apo-Captopril® 50mg Tab.	1	0.0015	143.48	0.0010	0.70
	CaptoHexal® 50mg Tab.	30	0.04	5 005.91	0.04	1.00
	Captomax® 50mg Tab.	389	0.57	54 213.22	0.39	0.68
	Captopril-acet® 50mg Tab.	24	0.04	1946.88	0.01	0.25
	CardiACE® 50mg Tab.	8	0.01	505.15	0.004	0.40
	Rolab-Captopril® 50mg Tab.	72	0.10	12 454.77	0.09	0.90
	Zapto® 50mg Tab.	95	0.14	13 006.15	0.09	0.64
Total innovator		365	0.54	135 322.43	0.98	-
Total generic		796	1.69	112 394.89	080	-

According to the classification of ACE inhibitors as innovator/generic drugs, Capoten® 50mg Tab. was identified as an innovator ACE inhibitor, with 8 alternative generic equivalents (Summarised in table 5.30). Among the large number of equivalents of Capoten® 50mg Tab. available, Captomax® 50mg Tab. has the highest prevalence (0.57%; n=68162) and cost (0.39%; n=R13863080.90). Capoten® 50mg Tab. is still highly prescribed with the prevalence of (0.54%; n=68162) and cost (0.98%; n=R13863080.90). All the agents in this group except for Capoten® 50mg Tab. and CaptoHexal® 50mg Tab. have cost index values that are lower than 1 thus indicating that these agents constitute relatively low costs. As already said above,

Capoten® 50mg Tab. and CaptoHexal® 50mg Tab. both have the cost index value greater than 1 thus implying that the cost of these two drugs is high.

Table 5.31 Cost analysis of Capoten ® 50mg Tab.and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Capoten® 50mg Tab.		365	370.75	131.48	2.04	573.48
	Adco-Captopril® 50mg Tab.	177	141.92	47.36	73.27	221.48
	Apo-Captopril® 50mg Tab.	1	143.48	-	-	143.48
	CaptoHexal® 50mg Tab.	30	166.86	57.50	40.99	224.56
	Captomax® 50mg Tab.	389	139.37	56.16	0.80	427.27
	Captopril-acet® 50mg Tab.	24	81.12	-	-	81.12
	CardiACE® 50mg Tab.	8	63.14	22.97	35.40	79.79
	Rolab-Captopril® 50mg Tab.	72	172.98	41.47	80.04	222.05
	Zapto® 50mg Tab.	95	136.91	34.17	0.80	222.13

A cost analysis of Capoten® 50mg Tab. and its alternative generic forms (depicted in table 5.31) indicates that Capoten® 50mg Tab. has the highest average cost (R370.75 ± R131.48) and maximum cost (R573.48) when compared to the average and maximum costs of its generics. It is the 2nd most popular agent of the group with the prevalence of (0.54%; n= 68162) whereas Captomax® 50mg Tab. is the most popular with the prevalence value of (0.57%; n=68162) with the average cost (R139.37 ± R56.16), it has a maximum cost of R427.27 which is the second-most highest of both the innovator and generic. Of the entire group, CardiACE® 50mg Tab. has the lowest average cost (R63.14 ± R22.97) and the maximum cost of R79.79 and still it is the least prescribed agent in this group with the prevalence of only (0.01%; n=68162).

R83 784.12 in cost could be saved if the total number of prescriptions for Captopril 50mg Tab. (both innovator and generics) were replaced with generics. The amount was derived from the following calculation: The total cost of all the Captopril 50mg Tab. (innovator and generics) (R247 717.32) minus the product of the usage cost per generic Captopril 50mg Tab. items (R112 394.89/796=R141.20) and the total number of Captopril 50mg Tab. items prescribed (365+796=1161). Thus R247 717.32–(141.20 x 1161) = R83 784.12.

Apart from being replaced with generics, the cheapest of all generics CardiACE® 50mg Tab. can be used as a replacement for Captopril® 50mg Tab. since they all have the same strength.

5.7.4. Captopril + Hydrochlorothiazide: innovator/generic analysis

5.7.4.1 Capozide® 50/25mg Tab.

Table 5.32 Prevalence, cost and cost index values of Capozide® 50/25mg Tab. and its equivalent generic.

Innovator	Generic	Prevalence	Prevalence (n=68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Capozide® 50/25mg Tab.		288	0.42	68 574.19	0.49	1.17
	Captoretic® 50/25mg Tab.	346	0.51	52 638.88	0.38	0.75
	Zapto co® 50/25mg Tab.	443	0.65	73 004.37	0.53	0.82
Total innovator		288	0.42	68 574.19	0.49	-
Total generic		789	1.16	125643.25	0.91	-

When analysing the data that were obtained from the medicine claims database it was found that all the generic agents have cost index values of less than 1, thus constituting relatively low costs in comparison to their specific prevalences whereas Capozide® 50/25mg Tab had a cost index of greater than 1 thus showing that its cost percentage is greater than its prevalence percentage (refer to table 5.32).

Table 5.33 Cost analysis of Capozide® 50/25mg Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Capozide® 50/25mg Tab.		288	238.10	44.57	88.18	484.86
	Captoretic® 50/25mg Tab.	346	152.14	31.26	1.56	314.88
	Zapto-Co® 50/25mg Tab.	443	164.80	46.11	1.71	315.38

It can be derived from the cost analysis, depicted in table 5.33 that the most popular drug in terms of prevalence is Zapto Co® 50/25mg Tab. (0.65; n= 68 162) with a relatively high average cost (R164.80 ± R46.11) and a high maximum cost (R315.38).

From the prevalence of both the innovator and generic drugs (0.42%; n=68 162) and (1.20%; n= 68 162) respectively, it can be concluded that this can be seen as positive utilisation of the generic forms of ACE inhibitors. Though it was found that if all the prescriptions containing Captopril 50/25mg Tab. were generically substituted, R22 715.96, could be saved. The amount was derived from the following calculation: The total cost of all the Captopril 50/25mg Tab. (innovator and generics) (R194 217.44) minus the product of the usage cost per generic Captopril 50/25mg Tab. items (R125 643.25/789=R159.24) and the total number of Enalapril 20mg Tab. items prescribed (288+789=1077). Thus R194 217.44– (159.24 x 1077) = R22 715.96.

5.7.5. Enalapril + Hydrochlorothiazide: innovator/generic analysis

5.7.5.1 Co-Renitec® Tab.

Table 5.34 Prevalence, cost and cost index values of Co-Renitec® Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Prevalence (n= 68 162) (%)	Cost (R)	Cost (n=R13 863 080.90) (%)	Cost index
Co-Renitec® Tab.		4 282	6.28	1 219 577.08	8.80	1.40
	EnapCo®Tab.	29	0.04	4 750.50	0.03	0.75
	Pharmapress Co® Tab.	430	0.63	90 439.06	0.65	1.03
Total innovator		4 282	6.28	1 219 577.08	8.80	-
Total generic		459	0.67	9 518956	0.68	-

When analysing the data that were obtained from the medicine claims database it was found that Co-Renitec® Tab. and Pharmapress Co® Tab. (innovator and generic) have cost index values greater than 1, thus these two drugs constitute relatively high costs in comparison to their specific prevalences (refer to table 5.34). Also, the innovator drug Co-Renitec® Tab. has a large prevalence in the data (6.28%; n= 68 162) and cost (8.80%; R13 863 080.90).

Table 5.35 Cost analysis of Co-Renitec® Tab. and its equivalent generics.

Innovator	Generic	Prevalence	Average cost (R)	Standard deviation (R)	Minimum cost (R)	Maximum cost (R)
Co-Renitec® Tab.		4282	284.81	32.37	48.18	608.55
	EnapCo® Tab.	29	163.81	4.99	161.48	174.54
	Pharmapress Co® Tab.	430	210.32	32.65	2.1	421.95

It can be derived from the cost analysis, depicted in table 5.35 that Co-Renitec® Tab. has the highest prevalence as stated above with a high average cost (R284.81 ± R32.37) and the high maximum cost (R608.55) whereas the next popular drug in terms of prevalence in the group is Pharmapress Co® Tab. (0.63%; n= 68 162) with a relatively high average cost (R210.32 ± R32.65) and a high maximum cost (R421.95).

It was found that if all the prescriptions containing (Enalapril + HCTZ) were generically substituted, R331 578.06, could be saved. The amount was derived from the following calculation: The total cost of all the (Enalapril + HCTZ) agents (innovator and generics) (R1 314 766.64) minus the product of the usage cost per generic Enalapril 20mg Tab. + HCTZ items (R95 189.56/459=R207.38) and the total number of Enalapril 20mg Tab. + HCTZ items prescribed (4282+459=4741). Thus R1 314 766.64 – (207.38 x 4741) = R331 578.06.

5.8. PREVALENCE AND COST OF ACE INHIBITOR ITEMS ACCORDING TO MONO-THERAPY AND DOUBLE COMBINATION THERAPY

5.8.1 Prevalence and cost of ACE inhibitor items that occur as mono-therapy.

A total sum of 67 341 prescriptions for mono-therapy of ACE inhibitor items occurred with the total cost amounting to R13 691 477.77. Thus 98.81% (n =68162) of the ACE inhibitor-containing prescriptions prescribed during the study period are cases where ACE inhibitors were prescribed as mono-therapy, representing 98.76% (n =R13 863 080.90) of the total cost of ACE inhibitors. Due to the large number of prescriptions containing a single ACE inhibitor item only the ACE inhibitors having the prevalence of greater than n=2000 will be analysed. These were the top eleven most frequently prescribed mono-therapies.

ACE inhibitor items were analysed according to a single entity, a product that has an ACE inhbitor and another drug e.g. a diuretic, in a single individual entity will be regarded as a single ACE inhibitor item e.g. Accuretic® which is a combination of an ACE inhibitor and a diuretic will be analysed as a single ACE inhibitor item since it is a combination of drugs in a single individual entity.

Table 5.36 represents the top eleven most frequently prescribed ACE inhibitor items that were prescribed as mono-therapy only, with an indication of the number of prescriptions containing the different ACE inhibitor item mono-therapies, the cost of the different mono-therapies, the prevalence and cost percentages as well as the cost index values.

Table 5.36 Prevalence, cost and cost index values of ACE inhibitor items utilised as mono-therapy.

ACE inhibitor Mono-therapy	Prevalence of mono-therapy prescriptions	Prevalence of mono-therapy prescriptions (n=67 341) (%)	Cost of mono-therapy (R)	Cost of mono-therapy (n=R13 691 477.77) (%)	Cost index
Renitec® 20mg Tab.	2 417	3.59	708 106.87	5.17	1.44
Renitec® 10 mg Tab.	2 381	3.54	412 150.55	3.01	0.85
Co-Renitec® Tab.	4 189	6.22	1 192 956.93	8.71	1.40
Coversyl® Tab.	10 243	15.21	2 185 508.39	15.96	1.05
Accuretic® 10/12.5 mg Tab.	2 696	4.00	393 529.17	2.87	0.72
Zestoretic® 20/12.5 mg Tab.	3 477	5.16	968 133.15	7.07	1.37
Accuretic® 20/12.5 mg Tab.	3 286	4.88	732 682.93	5.35	1.10
Zestoretic® 10/12.5mg Tab.	2 137	3.17	349 467.48	2.55	0.80
Tritace® 2.5 mg Tab.	2 695	4.00	487 317.86	3.56	0.89
Tritace® 5 mg.Tab.	3 166	4.70	837 223.34	6.11	1.3
Zestomax® 10 mg.Tab.	2 148	3.19	222 294.08	1.63	0.51
Total	**38 835**	**57.67**	**8 489 370.75**	**62.00**	**-**

The sum of the percentage columns does not add up to a hundred due to the fact that the total number of prescriptions (n=67341) for all mono-therapies was used to calculate the prevalence percentages. As is the case of the total cost percentages, where the sum (n=R13 691 477.77) of all mono-therapies was used to calculate the percentages.

It can be concluded, from table 5.36, that of the top eleven ACE inhibitor items most frequently prescribed as mono-therapy, Coversyl® Tab. has the highest prevalence

(n=10 243 prescriptions) with a cost of R2 185 508.39, followed by Co-Renitec® Tab. (n=4 189 prescriptions) with a cost of R1 192 956.93 and Zestoretic® 20/12.5 mg Tab. (n=3 477 prescriptions) with a cost of R968 133.15. A further demonstration of the prevalence and cost percentages will follow in figure 5.6 to ensure a clearer picture of the use of ACE inhibitor items as mono-therapy.

- The top eleven ACE inhibitor items most frequently prescribed as mono-therapy, are represented by the following numerical values in both figures 5.6 and 5.7:

1. Renitec® 20mg Tab.
2. Renitec ® 10mg Tab.
3. Co-Renitec® Tab.
4. Coversyl® Tab.
5. Accuretic® 10/12.5 mg Tab.
6. Zestoretic® 20/12.5 mg Tab.
7. Accuretic® 20/12.5 mg Tab.
8. Zestoretic® 10/12.5mg Tab.
9. Tritace® 2.5mg Tab.
10. Tritace® 5mg.Tab.
11. Zestomax® 10mg.Tab.

Figure 5.6 Prevalence and cost percentages of ACE inhibitor items utilised as mono-therapy.

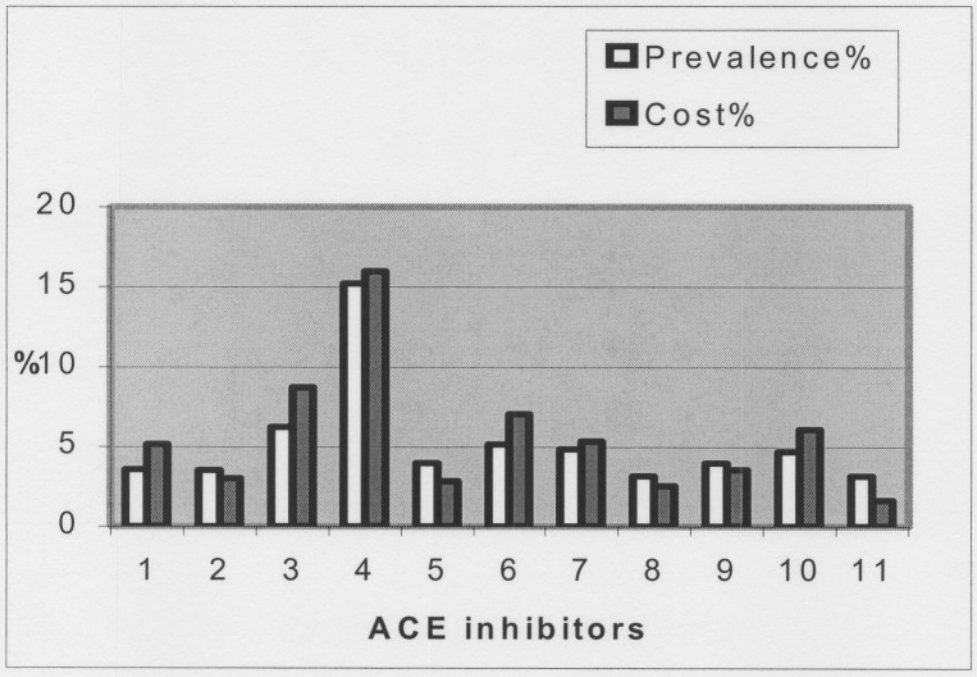


Figure 5.6 emphasises the high prevalence of Coversyl® Tab. (15.21% n=67 341). A contributing factor to the high prevalence of Coversyl® Tab. could be attributed to the

high prevalence of Perindopril (15.11%; n=68 162), the active ingredient of Coversyl® Tab. since it is the innovator drug with no generic equivalents (refer to table 5.13). However, ten of the top eleven ACE inhibitors, most frequently prescribed as mono-therapy are innovator drugs except for Zestomax® 10mg.Tab. that is a generic.

In the top eleven ACE inhibitor items most frequently prescribed as mono-therapy, only agents from catergory A (carboxyl) and category D (combinations group) are present. NB, the combinations group of ACE inhibitors is a drug that has an ACE inhibitor and another drug in one entity hence it was analysed as active ingredients in active ingredients 1-20), category B and category C are not present at all.

Figure 5.7 Cost index values of ACE inhibitor items utilised as mono-therapy.

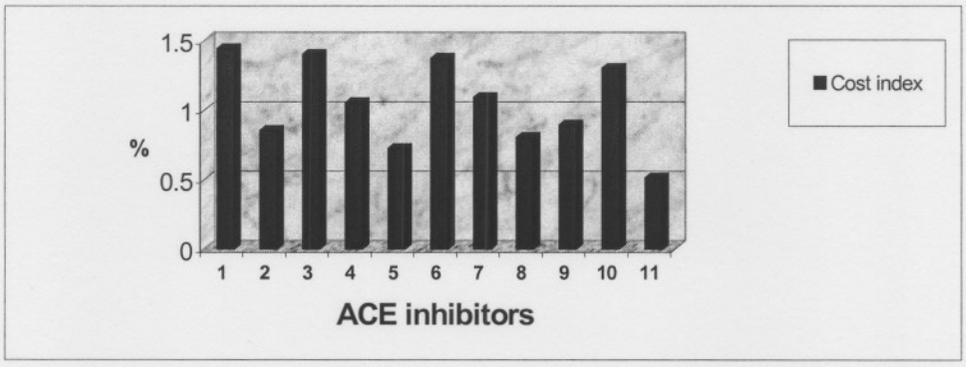


Figure 5.7 is an illustration of the cost index values of the top eleven ACE inhibitor items most frequently prescribed as mono-therapy. It can be derived from figure 5.7 that six out of eleven agents have a cost index value exceeding one, which is thus an indication of a relatively high cost in comparison with the prevalence of these agents.

5.8.2. Prevalence and cost of ACE inhibitor items that occur as double or combination therapy.

Double combination therapies of ACE inhibitor items have shown to have less prevalence when compared to the mono-therapy. The total prevalence of the double ACE inhibitor item combinations, amounted to n= 406 with the total cost thereof amounting to R171 603.13.

The analysis that follows, concerning the double ACE inhibitor combination therapy, is based on the top eleven ACE inhibitor combinations with the frequency greater than ten.

Table 5.37 Prevalence, cost and cost index values of ACE inhibitor items utilised as double combination therapy.

ACE inhibitor double combination therapy	Prevalence of combination per prescription	Prevalence of combination per prescription (n=406) (%)	Cost of double combination therapy (R)	Cost of double combination therapy (n=R171 603.13) (%)	Cost index
Capoten® 25mg Tab. + Capoten® 50mg Tab.	11	2.71	5 394.06	3.14	1.16
Renitec® 5mg Tab + Renitec® 10 mg Tab.	20	4.93	5 592.51	3.26	0.66
Renitec® 10mg Tab. + Renitec® 20 mg Tab.	13	3.20	6 026.24	3.51	1.10
Zestril® 10mg Tab. + Zestril® 5 mg Tab.	13	3.20	3 658.41	2.13	0.67
Accupril® 10mg Tab. + Accuretic® 20/12.5 Tab.	14	3.45	6 910.01	4.03	1.17
Capace® 25mg Tab. + Capozide® 50/25 mg Tab.	13	3.20	4 297.71	2.50	0.78
Captomax® 25 mg Tab. + Coversyl® Tab.	11	2.71	3 464.57	2.02	0.75
Adco-Captopril® 50mg Tab. + Tarka® Cap.	11	2.71	4 738.03	2.76	1.02
Co-Renitec® Tab. + Renitec® 20 mg Tab.	28	6.90	15 569.79	9.07	1.31
Co-Renitec® Tab. + Renitec® 10 mg Tab.	46	11.33	21 744.78	12.67	1.12
Co-Renitec® Tab. + Renitec® 2.5 mg Tab.	11	2.71	3 972.10	2.31	0.85
Total	**191**	**47.04**	**81 368.21**	**47.42**	**-**

The sum of the percentage columns does not add up to a hundred due to the fact that the total number of prescriptions (n=406) for all the double combination therapies (with a prevalence of n=11 or higher) was used to calculate the prevalence percentages. As is the case of the total cost percentages, where the sum (n=R171 603.13) of all double combination therapies (with a prevalence of n=11 or higher) was used to calculate the percentages.

Table 5.37 is a summary of the prevalence and cost, the prevalence and cost percentages and the cost index values of the top eleven ACE inhibitor items combinations. The combination of Co-Renitec® Tab. + Renitec® 10 mg Tab. has the highest prevalence per prescription 46 (11.33%; n =406) with a cost of R21 744.78 (12.67%; n =R171 603.13), followed by Co-renitec® Tab. + Renitec® 20 mg Tab.with a prevalence per prescription of 28 (6.90%; n= 406) and a cost of R15 569.79 (9.07%; n=R171 603.13) and Renitec® 5mg Tab + Renitec® 10 mg Tab. with a prevalence per prescription of 20 (4.93%; n=406) and a cost of R5 592.51 (3.26%; n=R171 603.13). Emphasis must be placed on the extensive use of Renitec® Tabs. in combination with another ACE inhibitor item as is clear in table 5.36, where Renitec® Tabs. are part of five of the top eleven ACE inhibitor items double combinations most frequently prescribed.

The top eleven ACE inhibitor items combinations, most frequently prescribed as double-therapy, are represented by the following numerical values in both figures 5.7and 5.8:

1. Capoten® 25mg Tab. + Capoten® 50mg Tab.
2. Renitec® 5mg Tab + Renitec® 10 mg Tab.
3. Renitec ® 10mg Tab. + Renitec ® 20 mg Tab.
4. Zestril® 10mg Tab. + Zestril ® 5 mg Tab.
5. Accupril® 10mg Tab. + Accuretic® 20/12.5 Tab.
6. Capace® 25mg Tab. + Capozide® 50/25 mg Tab.
7. Captomax® 25 mg Tab. + Coversyl® Tab.
8. Adco-Captopril® 50mg Tab. + Tarka® Cap.
9. Co-Renitec® Tab. + Renitec® 20 mg Tab.
10. Co-Renitec® Tab. + Renitec® 10 mg Tab.
11. Co-Renitec® Tab. + Renitec® 2.5 mg Tab.

Figure 5.8 Prevalence and cost percentages of ACE inhibitor items utilised as double combination therapy.

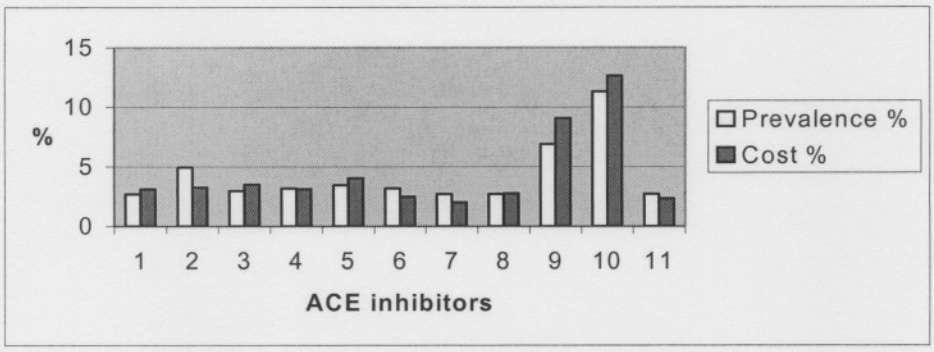
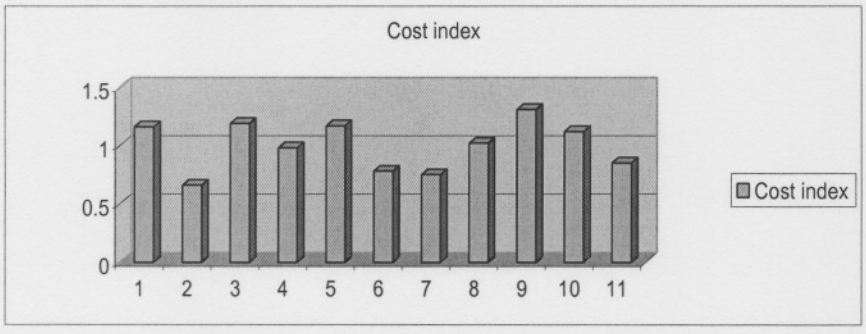


Figure 5.8 is an illustration of the prevalence and cost percentages of the top eleven ACE inhibitor item double combinations with the highest prevalence per prescription. Of the top eleven ACE inhibitor item double combinations, six have a cost percentage greater than the prevalence percentage. This alone is a conclusion that the cost of ACE inhbitor item double combination is expensive.

Figure 5.9 Cost index values of ACE inhibitor items utilised as double combination therapy.



According to the cost index values of the top ten ACE inhibitor item double combinations, represented in figure 5.8, the six combinations (refer to fig 5.8) have a cost index value greater than 1, meaning that the cost of these drugs is relatively high.

5.9 CHAPTER SUMMARY

In this chapter, the results of the empirical investigation have been discussed. An in-depth analysis of the prevalence of ACE inhibitor items, plus the costs that can be associated with ACE inhibitor items usage (according to the four-fold classification of the ACE inhibitors), have all been used to ensure that the aims, set specifically for the empirical investigation, have been achieved.

The conclusion and recommendations, based on the empirical inverstigation, will be formulated and discussed in chapter six.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The conclusions of the study, based on the results of the literature review and the empirical investigation, as well as the recommendations derived from this study on the analysis and usage patterns of ACE inhibitors will be discussed. A detailed discussion of the limitations encountered during the study is also included in this chapter.

6.2 CONCLUSIONS

In order to ensure that the study has succeeded in achieving the specific aims that were set, the conclusions drawn for each aim will be discussed briefly:

1. The first specific objective was to conceptualise the use of ACE inhibitors in the treatment of hypertension and congestive heart failure. (refer to paragraphs 2.3 and 2.4).

ACE inhibitors are now established therapy in two of the most common cardiologic conditions, namely hypertension and congestive heart failure. 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. 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 (refer to paragraph 2.1)

ACE inhibitors are a structurally diverse group of agents with similar therapeutic effects (refer to paragraph 2.3.6.4 and 2.4.5.3).The classification of ACE inhibitors is primarily based on its four-fold classification, constituting of:

- A chemical category classification consisting of four categories of ACE inhibitors, namely category A (Carboxyl group), category B (Sulphydril group), category C (Phosphonyl group) and category D (combination drugs consisting of a combination of an ACE inhibitor and a diuretic or calcium channel blocker).

- Different active ingredient classification. The active ingredient classification was found to be a group of 20 typical ACE inhibitor product items with the combinations included.
- Original or generic equivalents
- Different dosage quantities

2. The second specific aim was to investigate the methods and techniques that are utilised in health-care, in order to ensure cost-effective drug use.

In an in-depth literature review, pharmacoeconomics and pharmacoepidemiology were identified as playing an integral role in ensuring cost-effective health-care. The purpose of an economic evaluation is to provide a menu of choices together with a comparison between cost and outcomes associated with each choice. The increasing pressure for cost containment and a more equal balancing of costs, benefits and outcomes associated with health-care, have led to an increase in the importance of pharmacoeconomics. Whereas pharmacoepidemiology focuses mostly on the use and effects of drugs in a define population (refer to paragraphs 3.3 and 3.4).

The field of pharmacoepidemiology currently focuses on pharmaceutical care outcomes and the identification of potential or realised drug use problems, particularly the adverse effects of drugs (refer to paragraph 3.3). The use of pharmacoepidemiologic studies has great potential, playing an important role in drug utilisation reviews and providing the basis for pharmacoeconomic analyses. Its basic idea is to measure the source, use and effects of drugs in a specific population (refer to paragraph 3.3).

The field of pharmacoeconomics on the other hand is dedicated to the study of how different approaches to patient care and treatment influences the resources consumed in health-care. A pharmacoeconomic research is primarily driven by the basic principle that financial resources are limited and that the organisational needs generally exceeds the available resources. (refer to paragraph 3.4.1)

3. The third specific aim was to review the total cost of ACE inhibitor items derived from the data.

   By means of the analysis of the general medicine utilisation patterns that were obtained from the medicine claims database, it is evident that ACE inhibitor utilisation contributes considerably to the total prevalence and cost of all the medicine items available on the database. It constitutes a total prevalence of 4,62% (n =1 475 532) of all the prescriptions and a total prevalence of 2,31% (n =2 953 244) of ACE inhibitors in the prescriptions, with a cost of 3,65% (n =R379 911 472,00) for all the medicine items in the prescriptions (refer to paragraph 5.2).

4. The fourth specific aim was to determine the prevalence and usage patterns of ACE inhibitors as well as the costs associated with these drugs.

   The utilisation of the previously mentioned four-fold classification of ACE inhibitors compiled specifically for this study aided in a further analysis of the prevalence, usage and costs associated with the ACE inhibitors. Category A (Carboxyl) ACE inhibitors were identified as the category with the highest proportion of ACE inhibitor usage, which amounted to a prevalence of 57,99% (n =68 162) and at a cost of 55,59% (n =R13 863 080,90) (refer to paragraph 5.3.1). Due to the aspect of high prevalence and the fact that the Category A (Carboxyl) ACE inhibitors have a cost index value below 1, it can be concluded that the extensive usage of this category is warranted in comparison to the Category D (Combinations) ACE inhibitors. The latter is the second most prescribed category, amounting to a prevalence of 34,13% (n =68 162) at a cost of 39,07% (n =R13 863 080,90). It had a cost percentage higher than its prevalence percentage, with a cost index value of 1.14, meaning that its cost is relatively high.

5. The fifth specific aim was to identify and analyse the different innovator forms of ACE inhibitors with their different generic equivalents.

   Only five of the twenty active ingredients have generic equivalents. This amounted to a generic prevalence of 17,44% of the total database (n=68 162). Of the five active ingredients with generic equivalents, only two active ingredient innovator drugs have shown a positive

utilisation of generics, where generic equivalents were prescribed more than their innovator equivalents i.e Prinivil® tab and Capozide® tab.

6. The sixth specific aim was to determine the prevalence and costs associated with innovator and generic drugs of the ACE inhibitor agents.

In the analysis of ACE inhibitors according to the innovator/generic classification, it was found that the majority of ACE inhibitors prescribed during the twelve-month period were for the innovator product, with a prevalence of 82,56% (n =68 162) and a cost of 89,11% (n =R13 863 080, 90) (refer to paragraph 5.5.1). The utilisation of the generic ACE inhibitors, with a prevalence of 17,44% (n =68 162) and at a cost of 10,89% (n =R13 863 080, 90), was under-utilised. However, if the total number of prescriptions containing innovator ACE inhibitors could be generically substituted, (37,54%) R5 204 392,67 in cost expenditure could be saved over a twelve-month period (refer to paragraph 5.6). However, the fact that not all the innovator ACE inhibitors have generic equivalents available must be taken into account. If only the prescriptions containing all ACE inhibitors that have generic equivalents, i.e. (the only five in the database) were to be substituted with their generic equivalents, R899 751.29 (6.5%) would be saved. This was found by adding all the costs saved by substituting innovator drugs with thier generics.

It was found that Perindopril, an innovator drug was the most predominantly used active ingredient, having a prevalence of 15,10% (n = 68 162) with a cost of 15,84% (n =13 863 080,90) for the twelve-month period. Consequently, it can be concluded that the extensive use of the innovator ACE inhibitors could mean an exceptional increase in the cost expenditure associated with ACE inhibitor therapy.

7. The seventh specific aim was to identify combination (mono or double) therapy of ACE inhibitor items and to determine the costs associated with these combinations.

A total of 98,81% (n = 67 341) of the prescriptions issued (n = 68 162) were cases of ACE inhibitor monotherapy, which amounted to a total cost of 98,76% (n = R13 691 477,77) of the total amount on the database (n=13 863 080,90)(refer to paragraph 5.8.1). ACE inhibitor double combination therapy constituted the smallest majority of the ACE inhibitor-containing

prescriptions that were issued during the study period. Some 406 prescriptions containing double combination therapy with a cost of R171 603,13 were identified as having a prevalence of less than 1% on the overall database (refer to paragraph 5.8.2). The utilisation patterns of the different dosage quantities (strength) of ACE inhibitor drugs as well as the costs associated with these dosage quantities (strength) were determined.

8. The eighth specific aim was to formulate recommendations regarding the utilisation patterns of ACE inhibitor drugs (both innovator and generics).

In completion of the study, five recommendations were formulated as an aim to optimise the utilisation of ACE inhibitor-generic equivalents.

A further discussion of the recommendations will follow in paragraph 6.4.

6.3 LIMITATIONS OF THE RESEARCH STUDY

A number of limitations were encountered during the course of the research study. These limitations could possibly have an effect on the results and conclusions obtained in this study and should be taken into account when evaluating the results and conclusions. A detailed list of the limitations will follow to emphasise the importance of taking these limitations into account at all times.

- All the information concerning medicine usage and the cost of medicine usage obtained from the medicine claims database that was utilised as data source in this study was considered to be accurate and correct.
- No demographic or clinical data concerning the gender, age or diagnoses of the study population was available on the database, thus making finer categories of the study population impossible.
- The amounts and percentages derived from the database are only valid for the specific medicine claims database that was utilised for the purposes of this study. Therefore, it cannot be used as a true indication of ACE inhibitor usage patterns nor will it reflect the true costs of ACE inhibitor usage in the whole of South Africa.

- The analysis on the mono and double combination therapy included the active ingredients, with the combination group being included as a single drug therapy.

6.4 RECOMMENDATIONS

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

- A uniform database should be developed to facilitate longitudinal observation, the documentation of disease features and comparison among populations of patients with cardiovascular diseases. The database should include standardised radiographic, pathological, clinical and economic information. The necessity to develop advanced databases, which are able to integrate economic and clinical data to be applied in drug utilisation reviews, is strongly recommended.
- The current disease management programmes should make provision for ACE inhibitors to be generically substituted in order to save the total cost by 11%.
- More studies are needed to compare the effectiveness of ACE inhibitors between the different active ingredients.
- The simultaneous use of ACE inhibitors should be reviewed, especially in combinations containing two different active ingredients of the same category. A review encompassing the clinical and economical aspects of the newer ACE inhibitors, with particular reference to the advantages of these ACE inhibitors, is recommended.
- The need for adequate public and professional education concerning generic ACE inhibitor usage is emphasised and is strongly recommended as a future aim for health-care departments in South Africa.

6.5 CHAPTER SUMMARY

In this chapter, the conclusions of the specific aims of the study were drawn and discussed. The recommendations that were derived in completion of the study, as well as the limitations that were encountered during the course of the study, were discussed.

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