The treatment of asthma: A managed pharmaceutical care approach

Pieter Johannes Kilian

B.Pharm

Dissertation submitted in fulfilment of the requirements for the degree Magister Pharmaciae at the North-West University, Potchefstroom Campus.

Supervisor: Mr. W.D. Basson

Co-supervisor: Dr. DM Rakumakoe

POTCHEFSTROOM

NOVEMBER 2005

ACKNOWLEDGEMENTS

I gratefully extend my sincere gratitude to the following people and institutes who helped and guided me to make this study possible:

- The Almighty, giving me strength and perspective to finish this study.
- Mr. Basson, in his capacity as supervisor of this dissertation.
- To the department of Pharmacy practice and its personnel for the moral and financial support during the completion of this study.
- Prof. Martie Lubbe, my appreciation for her expert guidance and assistance during this study.
- Prof. Jan Serfontein, for his advice regarding the study.
- The NRF® for financial support during this study.
- Interpharm Data Systems® for the data provided during this study.
- All my friends in De Wilgers for their friendship and support especially Ryno Steyn, Johann van der Walt, Derek Venter, Dewald de Beer, Johan van der Westhhuizen, Retief van der Walt and Etumaleng Bapela.
- Prof. Hans and Elsie De Ridder for their friendship, support and faith in me.
- My family, for their constant encouragement, love and support.
- Carla for her love, encouragement, support and faith in me.

Abstract

During 2004 the South African Pharmaceutical sector experienced a drastic change in the pricing system of pharmaceuticals.The aim of this study was to analyse the usage and cost associated with asthma medication according to a medicine claims database.

A quantitative retrospective drug utilisation research design was used to evaluate the usage patterns and costs associated with asthma-related drugs. The asthma-related drugs included for this study were the bronchodilators and the anti-asthmatics. The data for one year (1 January 2004 to 31 December 2004) were extracted from a medicine claims database. The study period was divided into three time periods, namely January to April, May to August and September to December. From January to April there were no limitations on the pricing structure of medicine (pre-single exit price). The new legislation came into effect in May 2004 and changed the pricing structure of medication. May to August is referred to as the interim period, where the new regulations was to be phased in. As from September 2004 the new pricing regulation was "fully" implemented, therefore September to December can be referred to as the post-single exit price period.

Asthma is diagnosed on the basis of certain signs and symptoms, which can be substantiated by a clinical investigation. Asthma medicine represented 4.46% (N = 115 684) of medicine prescribed on the medicine claims database (N = 2 595 254) and 18.40% of all respiratory system medicine (N = 628 754). In comparison with the total database (33.49%, N = 5 305 882), the generic substitution of asthma medication is far less, representing 24.18% of medication prescribed for asthma. The data clearly indicate the decrease in average price per item for both groups of asthma-related medication. The price showed a decrease of 19.53% with the implementation of the single exit price for the bronchodilators and 10.40% for anti-asthmatics. A further decrease from the SEP price of the bronchodilators and the anti-asthmatics, respectively 14.74% and 13.64%, indicates the price reducing effect of the legislation on medicine cost.

Abstrak

Gedurende 2004 het die Suid Afrikaanse Pharmaseutiese sektor drastiese veranderinge ondergaan in die prysstrukture. Die doel van die studie was om die verbruik en die koste wat met asma geassosieer word volgens 'n medisyne databasis te bepaal.

'n Kwantitatiewe retrospektiewe navorsing studie was gebruik om die verbruiks patrone en kostes geassosieer met asma geassosieerde medikasie te bepaal. Die asma medikasie in die studie ingesluit was die brongodilators en die anti-asmatiese medikasies. Die data vir een jaar (1 Januarie 2004 tot 31 Desember 2004) is ontrek van die medikasie databasis. Die studie periode is opgedeel in drie tydsvakke, nl. Januarie tot April, Mei tot Augustus en September tot Desember. Vir Januarie tot April was daar geen beperkings op die prys strukture van medikasie. Die wetgewing het in Mei 2004 aanvang geneem en die prysstrukture van medisyne verander. Mei tot Augustus was die iterim periode, waar die nuwe regulasies ingefaseer is. Van September 2004 is die nuwe prysstrukture ten volle geimplementeer.

Asma word gediagnoseer op grond van tekens en simptome, wat verkry kan word van kliniese ondersoeke. Asma medikasies verteenwoordig 4.46% (N = 115 684) van medikasie medikasie voorgeskryf op die medisynebasis (N = 2 595 254) en 18.40% van die respiratoriese sisteem medisyne (N = 628 754). In vergelyking met die totale databasis 33.49% (N = 5 305 882), het generiese substitusie medikasie minder verteenwoordige met 24.18% van die voorgeskrewe asma medikasie. Die data wys 'n verlaging in gemiddelde prys per item vir beide groepe van asthma medikasie. Die pryse wys 'n verlaging van 19.53% met die implementasie van die nuwe prys regulasies vir die brongodilators en 10.40% anti-asmatiese medikasie. 'n Verdere verlaging van die SEP van die brongodilators en die anti-asmatiese medikasie,dui onderskeidelik op 14.74% en 13.64%.

TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

The focus of this dissertation is on the medicine management of asthma according to a medicine claims database. Data of 2004 will be used to investigate the medicine treatment patterns of asthma in the private health care sector in South Africa.

1.2 PROBLEM STATEMENT

Asthma is a serious health problem. It is one of the most costly conditions, and has a substantial impact on health, quality of life of patients and the economy in general (Centre of Disease Control 2003). Asthma is one of the most common respiratory conditions in the world today. It affects one in ten children and one in twenty adults, and can occur for the first time at any age even in adulthood, although it usually begins at the age of five years. Half of the children affected will "outgrow" it during their teenage years but it usually persists if contracted in adulthood (Jeena *et al.*, 2003).

Asthma is a condition affecting the airways or the bronchi of the lungs. The bronchi are lined with a thin layer called mucosa. Around the mucosa lie mucus-producing glands, cartilage to hold the airways open and surrounding these are muscle bands. In an attack of asthma, the mucus glands become swollen and secrete profuse thick mucus. This swelling accompanied by extensive secretion is called inflammation. When inflammation is present the muscle band becomes irritable and goes into spasm. This further causes narrowing or even blockage of the bronchi, thus producing the symptoms of asthma (National Department of Health, 2003)

The goal of asthma treatment is to minimise symptoms, exacerbations, use of rescue medication and adverse effects from medication and to maintain near normal peak expiratory flow values and normal activity levels (National Asthma Campaign, 2005).

Medication, regular control and medical consultations for acute exacerbations are expensive. In some countries, medical expenses are largely covered by medical insurance (Lacroix *et al.*, 1995: 305). Days away from work with the eventual loss of jobs may contribute to financial burden. Apart from financial costs there are also psychological, professional, family and social costs to consider (Lacroix *et al.*, 1995: 305).

Though asthma prevalence continues to receive a significant amount of attention, it is only part of a larger story about the asthma crisis. Equally important is the tremendous – yet largely preventable – impact of poorly managed asthma (American Lung Association, 2002).

In addition to the cost of asthma to individuals, the condition also takes a serious toll on the economy and the health care system in general. In 2002 in the USA, the estimated direct and indirect cost of asthma was $12.7 billion; of which $4.6 billion was in lost earnings due to illness and death because of asthma. Direct medical costs for asthma amounted to an estimated $8.1 billion per year (Cisternas *et al.,* 2003:1212).

Surveys reveal that people suffering from asthma have inadequate understanding of their condition and the proper way to manage it (Sculpher *et al.,* 2002: 507). They also tend to underestimate the severity of the condition and overestimate its possible level of control (Sculpher *et al.,* 2002: 511).

Asthma management guidelines developed by the National Heart, Lung, and Blood Institute of America establish clear goals for asthma therapy that address many of the impact measures outlined above (American Lung Association, 2002).

By outlining an evidence-based approach to effective asthma management, the guidelines provide a powerful roadmap for decreasing mortality, emergency department visits and hospitalisation; reducing absence from work or educational institutions and improving health and quality of life for millions of people (American Lung Association, 2002).

According to the American Academy of Allergy Asthma and Immunology (2002) asthma medication can be divided into two groups. The first is the long-term control medication, which includes inhaled corticosteroids, cromolyn and nedocromil, theophyllin, leukotrine modifiers and long acting beta agonists. The second group includes quick relief medication such as short acting beta agonists and the systemic corticosteroids.

The importance of formal economic analysis in asthma care is, in part, a reflection of the disease in terms of reflection of the burden of the disease in terms of resource cost and health. Economic evaluation is a set of formal analytic techniques to establish the efficiency of alternative policy options and assist with priority settings (Sculpher *et al.,* 2002: 507)

Economic evaluation is also needed as a result of the development of new forms of management, such as pharmaceutical therapies, which often impose extra cost on the health care system but promise additional health benefits to patients (Sculpher *et al.,* 2002: 507).

In general South Africa is facing problems in both the public and private health care sectors. Health care expenditure has been one of the fastest growing sectors of the South African economy. Medicines consume a considerable large part of the health care expenditure in the country (Department of Health, 1998: 245). Control of health care expenditures in the next decade will be one of the major challenges facing the South African economy. In the private sector, medicine is the single major cost driver. During 1998, medical schemes paid out a total of R18.745 billion of which medicine accounted for 27% (Department of Health, 1998: 245). However, of the 28.5% of payments that were made to private hospitals, some were also for medicines used by inpatients and issued as discharge medication. Despite substantial spending on medicine, lack of access to essential medicine, irrational use of medicine, and poor quality remain serious global public health problems (Brundtland, 1999).

The burden of diseases in the private health care sector was measured by the Council of Medical Schemes (2002:48) through the prevalence of the top twenty chronic conditions. The data showed that asthma occurred in 24.6 out of a 100 cases (Council for Medical Schemes, 2002: 48).

In an attempt to contain rising pharmaceutical expenditures in the private health care sector, different mechanisms have been implemented such as generic substitution, a pricing system, prescribed minimum benefits and formularies.

On the 4th November 2002, changes to the Regulation of the Medical Schemes Act (Act no. 131 of 1998) were published, some of which have been implemented in 2003. On 1 January 2004 the remaining changes to the Regulation were implemented which included the introduction of Prescribed Minimum Benefits (PMBs) of the Chronic Disease List (CDL). The Chronic Disease List is a list of 27 chronic conditions, which have to be covered by all medical schemes from January 2004. Asthma is one of them.

The Prescribed Minimum Benefits are minimum benefits which by law must be provided to all medical scheme members,including the provision of diagnosis, treatment and care costs for a range of conditions specified in the regulations of the Medical Schemes Act (No. 131 of 1998). The prescribed minimum benefits for the chronic disease list (CDL) differ from the general list of prescribed minimum benefits in that their minimum treatment is specified in the therapeutic algorithms that have been legislated for each condition.

Another factor that might influence the usage and cost of anti-asthmatic agents is generic substitution. The average cost of some generic medicine is lower than that of the innovater/original medicine (Buehler, 2004).

From the foregoing discussion it is evident that the influence of generic substitution, prescribed minimum benefits, usage patterns and cost of anti-asthma agents must be investigated.

1.3 RESEARCH QUESTIONS:

Based on the foregoing discussion, the following research questions arise:

- What is the prevalence of asthma in the general public of South Africa?
- What does asthma as well as the management thereof entail?
- Which pharmaceutical care principles should be followed in the management of asthma?
- What do pharmaco-economic implications entail?
- What does pharmaco-epidemiology entail?
- What is the spectrum of medicine treatment of asthma and how did it change?
- What is the usage and cost of the different anti-asthmatic agents?
- What are the relevance and the frequency of generic substitution of the different categories of anti-asthmatic agents?
- What is the influence of the "new pricing system" in SA on the cost of anti-asthmatic agents?
- Which recommendations may be formulated regarding the usage of anti-asthmatic agents?

1.4 RESEARCH OBJECTIVES

The research embodies a general objective as well as specific objectives.

1.4.1 GENERAL OBJECTIVE

The general objective of this study was to review the medicine management of asthma in the private health care sector in South Africa through a managed pharmaceutical care approach.

1.4.2 SPECIFIC OBJECTIVES

Based on the research questions, the specific research objectives are as follows:

- To investigate the prevalence of asthma in the general public of SA.
- To conceptualise, through a literature study, what asthma together with its management entails.
- To determine which pharmaceutical care principles should be followed in the management of asthma.
- To determine the spectrum of anti-asthmatic agents and how it has changed through the years.
- To conceptualise what pharmaco-economic implications entail.
- To conceptualise what pharmaco-epidemiology entails.
- To determine, through a literature study, the cost of the medical treatment of asthma.
- To determine the relevance and frequency of generic substitution of the different categories of anti-asthmatic agents by using a medicine claims database.
- To determine the usage and cost of the different anti-asthmatic agents according to a medicine claims database.
- To investigate the influence of the new medicine pricing system on the cost of anti-asthmatic agents by analysing data of a medicine claims database.
- To compare the prevalence of asthma medication of 1995 with the prevalence of asthma medication of 2004.
- To investigate the rationality of combination asthma therapy.

1.5 RESEARCH METHOD

The research project consisted, in conjunction with the specific research objectives, of two phases namely a literature review and an empirical investigation.

1.5.1 PHASE ONE: LITERATURE STUDY

The literature study was divided into two steps. The first step was to gather information on asthma and the pharmaceutical care management thereof.The second step was to focus on the medicine cost of asthma in South Africa, managed care, pharmaco-economics and drug utilisation review.

Attention was paid to diagnosis, pathogeneses and complications as well as the pharmaceutical care management of asthma.

Managed care, pharmaco-economics and drug utilisation were defined and relevant principles on the usage patterns of anti-asthmatic agents investigated. Factors that contribute to the high cost of medicine in the private health care sector in South Africa as well as mechanisms that were implemented to contain rising pharmaceutical expenditure were considered.

1.5.2 PHASE TWO: EMPIRICAL INVESTIGATION

This phase consisted of five phases, namely:

- The selection of the study population.
- The selection of the measuring instruments.
- Data analysis.
- The report and discussion of the results of the empirical investigation.
- Recommendations based on the results of the empirical investigation.

A retrospective drug utilisation study was conducted on data provided by a pharmacy benefit company in South Africa. The data for this study were extracted from the database *Interpharm* Datasystems® in South Africa for a 12 months period, from the 1st January 2004 to 31st December 2004. Data were analysed with the aid of the *Statistical Analysis System* (SAS for Windows, 9.1, 2003) 8.2® computer package.

Comparisons and analyses were done on a four-monthly basis for 2004, using the Statistical Analysis System (SAS for Windows, 9.1, 2003). The asthma-related drugs included for this study were the bronchodilators and the anti-asthmatics.

Prevalence, average costs and standard deviations were calculated for the individual medicine, pharmacological groups, innovator medicine and generic medicine.

1.6 DIVISION OF CHAPTERS

Chapter 1: Introduction
Chapter 2: Managed pharmaceutical care principles applied to asthma
Chapter 3: Health care concepts applied to asthma treatment
Chapter 4: Research method
Chapter 5: Research discussion
Chapter 6: Conclusion, recommendations and limitations

1.7 CHAPTER SUMMARY

In this chapter the problem statement, research questions and objectives, research methodology, research design and division of chapters were discussed.

The management of asthma will be discussed in chapter 2.

CHAPTER 2

MANAGED PHARMACEUTICAL CARE PRINCIPLES APPLIED TO ASTHMA

2.1 INTRODUCTION

In this chapter an overview of the pharmaceutical care management of asthma will be given. The significance of an assessment plan will also be reviewed. The classification of the drugs used, adverse effects of asthma treatment, the management of these effects and the barriers in the management of asthma will be discussed.

2.2 PHARMACEUTICAL CARE DEFINED

Pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs, and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes (Cipolle *et al.,* 1998: 13). Pharmacists in both community and hospital practice are well placed to provide continued information and reinforcement of key messages to improve compliance with medication and the outcomes of asthma management plans (Bouyter *et al.,* 2000: 551).

Pharmaceutical care involves the pharmacist in three major functions on behalf of the patient: identifying potential and actual drug-related problems, resolving actual drug-related problems, and preventing potential drug-related problems (American Society of Consultant Pharmacists, 1998). A drug-related problem is an event or situation involving drug therapy that actually or potentially interferes with an optimum outcome for a specific patient (American Society of Consultant Pharmacists, 1998).

Pharmaceutical care is a new professional practice that has evolved from many years of research and practice in the profession of pharmacy. This new professional practice is not intended to replace the role of the physician or any other practitioner but rather to meet a need in the health care system that has arisen because of multiple prescribers of medication for a single patient, the explosion of drug products and drug information presently on the market, the increased complexity of drug

therapy, the significant level of drug-related morbidity and mortality associated with drug use, and the high human and financial cost of drug adventuring (Cipolle *et al.,* 1998: 13).

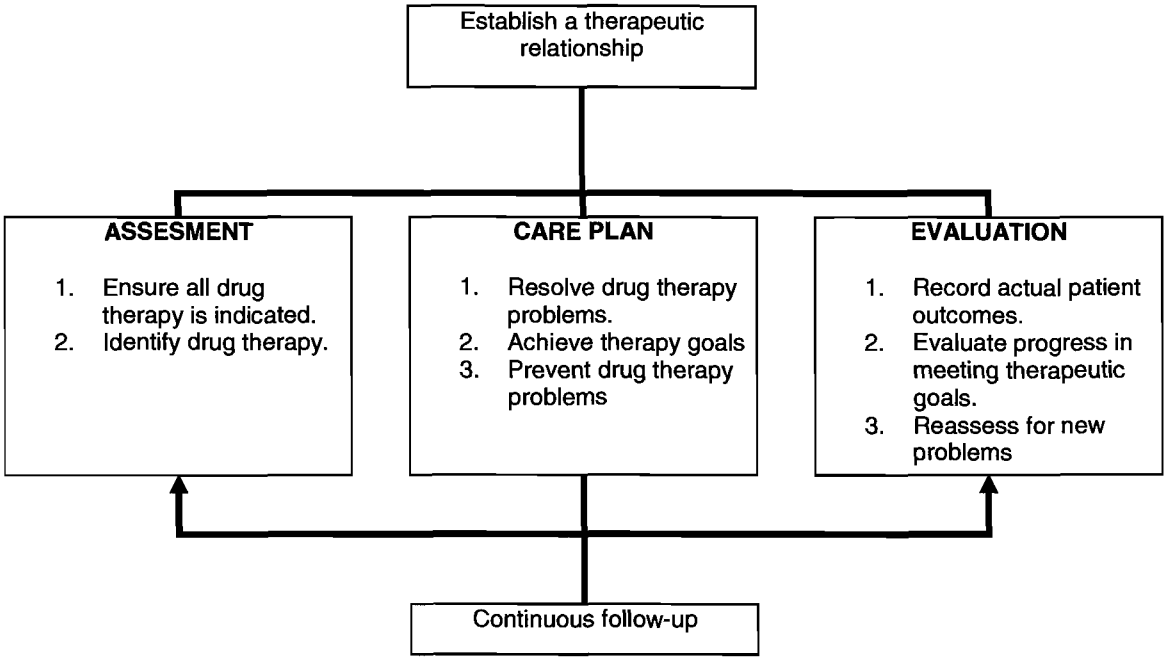
Drug-related problems include:

1. Untreated indications
2. Improper drug selection
3. Sub-therapeutic dosage
4. Over dosage
5. Adverse drug reactions
6. Drug interactions
7. Failure to receive medication
8. Drugs used without indication
9. Treatment failures (American Society of Consultant Pharmacists, 1998).

To effectively meet the social need of the patient, it is necessary for the practitioner of pharmaceutical care to use a patient centred approach to practice. This approach considers the patient as an individual whose particular health care needs generally and drug-related needs specifically are the primary concern of the practitioner. A patient centred approach means that all of the patient's drug-related needs are seen as the responsibility of the practitioner, not only those needs representing a specific drug category or a specific disease state (Cipolle *et al.,* 1998: 19).

Pharmaceutical care practice makes an individual responsible for the drug-related needs of patients in such a way that effective drug therapy can be offered according to a rational and systematic approach and be monitored in detail, *i.e.*, drug therapy together with all possible drug therapy problems, whether actual or potential, But even more important, pharmaceutical care practice requires the practitioner to prevent drug therapy problems from developing in the first place (Cipolle *et al.,* 1998:19).

Figure 2.1 The Pharmaceutical Care process (Roussell, 1998: 875)



Al-Shaqha *et al.* (2001: 291) define the pharmaceutical care process as three major steps:

Step 1: The pharmacist completes an assessment of the patients' drug-related needs, including identification of any drug therapy that exists or need to be prevented in the future.

Step 2: Pharmacists and patients work together to construct a care plan that should meet the goals of patients' therapy.

Step 3: The last major step – the pharmacist schedules and conducts a follow-up evaluation to determine the actual patient outcomes that have resulted from the care provided.

This makes the responsibility of the pharmacist in providing pharmaceutical care much greater. The pharmacist is responsible for the provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are: cure of a disease, elimination or reduction of a patient's symptomatology, arresting or slowing of a disease process or preventing a disease or symptomatology (American Society of Consultant Pharmacists, 1998).

Although collectively those in the health care arena have been slow to recognise the magnitude and scope of the problem of drug use, numerous attempts have been made to influence the use of drug therapy positively. For example, politicians have tried to control the non-medical use of drugs (illicit drug use) as well as the medical use of drugs (prescription/non-prescription designations). Control at this level has brought attention to the problems associated with drug use (Cipolle *et al.,* 1998:6).

2.3 THE PATIENT CARE PROCESS

Pharmaceutical care can be delivered in primary or secondary care, in the pharmacy or in the general practitioner practice, in the clinic or in the patient's home. Where it is delivered is not important, but how it is delivered and the thinking behind it. The pharmaceutical care process has three phases; the assessment, care plan, and evaluation. This model reflects the medical and nursing approach to delivering care. In all these models the needs of the patient are first assessed, resource treatment is given and the outcomes are evaluated (Pharmacy audit, 2000).

There is only one patient care process in pharmaceutical care, just as there is only one standard process for providing medical care, dental care, or nursing care (Cipolle *et al.,* 1998: 121). A common patient care process allows the process to be described explicitly so all practitioners can consistently practise it. Also, when practices have multiple pharmacists caring for patients, they are able to communicate easily amongst themselves (Cipolle *et al.,* 1998: 121).

2.3.1 ASSESSMENT

To carry out a comprehensive assessment of the drug-related needs of a patient, the practitioner must accomplish two objectives: (i) to collect, collate, and integrate several categories of patient specific data and (ii) to make the following decisions :

- Determine that all of a patient's drug therapy is the most appropriate, most effective, the safest, and the most convenient that is available for the patient.
- Identify any drug therapy problem that might be interfering with the goals of therapy.
- Identify any drug therapy problems that the pharmacist must help the patient to prevent in the future (Cipolle *et al.*, 1998: 132).

The collection of data is important because for, *inter alia*, the foolowing reasons:

- The pharmacist conducts an interview with the patient for the purpose of establishing a professional working relationship and initiating the patient's pharmacy records. In some situations (e.g. pediatrics, geriatrics, critical care, and language barriers) the opportunity to develop a professional relationship with and collect information directly from the patient may not exist (Cairns *et al.*, 2000: 136) (American Society of Consultant Pharmacists, 1998).

- The interview is organised, professional, and meets the patient's need for confidentiality and privacy. Adequate time is devoted to assure that questions and answers can be fully developed without either feeling uncomfortable or hurried. The interview is used to systematically collect patient-specific subjective information and to initiate a pharmacy record which includes information and data regarding the patient's general health and activity status, past medical history, medication history, social history, family history, and history of present illness. The record should also include information regarding the patient's thoughts or feelings and perceptions of his/her condition or disease (Cairns *et al.*, 2000: 137) (American Society of Consultant Pharmacists, 1998).

- The pharmacist uses health/physical assessment techniques (blood-pressure monitoring, etc) appropriately and as necessary to acquire necessary patient specific objective information (Cairns *et al.*, 2000: 137).

- The pharmacist uses appropriate secondary sources to supplement the information obtained through the initial patient interview and health physical assessment (Cairns *et al.*, 2000: 137).

- The pharmacist creates a pharmacy record for the patient and accurately records the information collected (Cairns *et al.*, 2000: 138).

After a person has sought medical care for symptoms that suggest asthma, the diagnosis of asthma should be clearly established and the baseline of severity (as discussed in section 2.4) of the disease classified to help establish the course of therapy (Storms, 2003: 534).

2.3.2 CARE PLAN

The pharmacist designs, implements, and monitors a pharmaceutical care plan for each patient who identifies desired therapeutic and/or functional outcomes for each medication prescribed and potential and/or actual drug-related problems. The pharmacist assesses the patient at appropriate intervals for progress toward the therapeutic and/or functional goals, and the occurrence and resolution of dru-related problems. The pharmacist continuously updates the pharmaceutical care plan with patient specific information and recommends modifications in therapy. The care plan is separate from, but developed in conjunction with, the patient's overall plan of care, if one exists (American Society of Consultant Pharmacists, 1998).

The care plan functions as a structure for working together with individuals who may have different levels of drug awareness and different values, expectations and understanding of the pharmaceutical care process and its responsibilities. Most often the care plan serves as an agreement or a "joint venture" between the patient and the practitioner. In the case where care is provided using a team approach, the team functions as a single entity. During the care-planning portion of the pharmaceutical care process patient specific goals are established, and decisions concerning which interventions would be appropriate for the patient are made. As a blueprint for pharmaceutical care, the care plan includes what must be accomplished to meet the patient's drug-related needs, when this should be accomplished, and how specific goals will be achieved in terms of interventions (Cipolle *et al.,* 1998: 154).

The goal of disease management is to produce the best clinical outcome with an acceptable risk/benefit ratio. For patients with asthma the National Institute of Health Expert Panel Report 2 (1997) on the diagnosis and management of asthma, outlines 6 general goals of therapy as discussed in table 2.1.

Table 2.1 Goals of therapy

1. Prevent chronic and troublesome symptoms.
2. Maintain (near) normal lung function.
3. Maintain normal activity level.
4. Prevent recurrent exacerbations and the need for emergency department visits or hospitalisation.
5. Provide optimal pharmaco-therapy with minimal adverse effects.
6. Meet the expectations and satisfaction of patients and family with care.

The patient's interestsare foremost, but regulators, payers, employers and providers are also important constituents in clinical decision making. Patients want a pharmaceutical plan that will cure disease and/or improve functioning and quality of life (Stempel *et al.,* 2002: S504).

The achievements of asthma control are related to improvements in health related quality of life. Overall and individually Asthma Quality of Life Questionnaire (AQLQ) domain (symptoms, emotional function, activity limitation and environmental stimuli) were assessed in some of the clinical trials of salmetarol/fluticasone propionate in persistent asthma. A change of more than 0.5 points overall or domain scores are considered clinically meaningful (Lyseng-Williamson *et al.,* 2003: 956).

According to Williams *et al.* (2003) the essential components of care and associated key clinical activities can be listed as follow:

1. Establish asthma diagnosis.
2. Classify severity of asthma.
3. Schedule routine follow-up care.
4. Assess the condition of the patient for the referral to speciality care.
5. Recommend measures to control asthma trigger factors.
6. Treat or prevent all co-morbid conditions.
7. Prescribe medication according to severity of asthma.
8. Monitor the use of $beta_2$-agonist drugs.
9. Develop a written asthma management plan.
10. Provide routine education on patient self-management.

Asthmatic patients may benefit from the introduction of self-management plans which provide an individually tailored care plan to cope with variations in their asthma severity. These plans, based on peripheral expiratory flow rate (PEFR) monitoring and symptoms recording, allow patients to alter their drug therapy without consulting health care providers or hospital consultants. They may include the administration of short courses of oral corticosteroids or an increase in the dose of inhaled corticosteroid and are normally instituted when the patient's PEFR falls below 80 per cent of the predicted or best value. It must be stressed, however, that when symptoms continue to deteriorate, patients should seek specialist help (Boyter *et al.,* 2000:553). Table 2.2 indicates the development of a pharmaceutical care plan. The knowledge needed, thought process and decision points are listed.

Table 2.2 Development of a pharmaceutical care plan (Makoid, 1999: v)

Knowledge needed	Thought Process	Decision point
Basic biological sciences Pathophysiology Physical assessment Thinking abilities Communication abilities	Investigate signs, symptoms, medical history, present illness; Determine need for therapy	Indication for therapy
Basic pharmaceutical sciences Medical chemistry Pharmacotherapy Pharmacodynamics Therapeutics	Review; translate into therapeutic effects; evaluate risk vs. benefits; set therapeutic endpoints	Selection of drug
Basic pharmaceutical sciences Pharmaceutics Pharmacokinetics Patient social and ethnicity awareness	Determine appropriate product formulation, dosage form, method of administration, dose, dosing interval, and duration based on patient parameters	Monitoring parameters
Basic clinical abilities: Integration of facts on: • Patient status • Disease state • Drug treatment • Laboratory data • Physical assessment	Review subjective and objective data collected; interpret if therapy is reaching therapeutic endpoints, causing toxicity, causing adverse effects	Monitoring therapy
Basic clinical abilities: • Pathophysiology • Pharmacotherapy • Problem solving • Decision making • Values and ethnical principles • Personal awareness and social responsibility	Evaluate outcome of therapy for effectiveness, ineffectiveness, adversity	Evaluation of therapy

It is reasonable to expect that the pharmacist would be able to develop a pharmaceutical care plan showing efficacy and possible toxicity which will set the course for therapy based on pharmacodynamic and therapeutic processes; select the

most appropriate regimen based on pharmacokinetics and pharmaceutical processes; determine how to monitor the therapy based on anticipated endpoints and outcomes; evaluate results based on outcomes; and decide to continue, alter, or discontinue therapy (Makoid, 1999: iv).

2.3.3 THE FOLLOW-UP EVALUATION

An essential step in the provision of pharmaceutical care is the follow-up evaluation. The evaluation is used to compare the desired therapeutic goals with the patient's present status. For acute disorders, the follow-up evaluation can serve to evaluate the actual (final) patient outcome; however, for patients with chronic conditions follow-up evaluations can only establish the present status of the patient and the progress or lack of progress in achieving desired therapeutic goals (Cipolle *et al.*, 1998: 160).

The follow-up evaluation process ensures the continuity of care. In practice, many patients have chronic disorders, which require continuous care and serial follow-up evaluation in order to compare the previously stated goals (Table 2.1) with patient progress (Al-Shaqha, 2001:295).

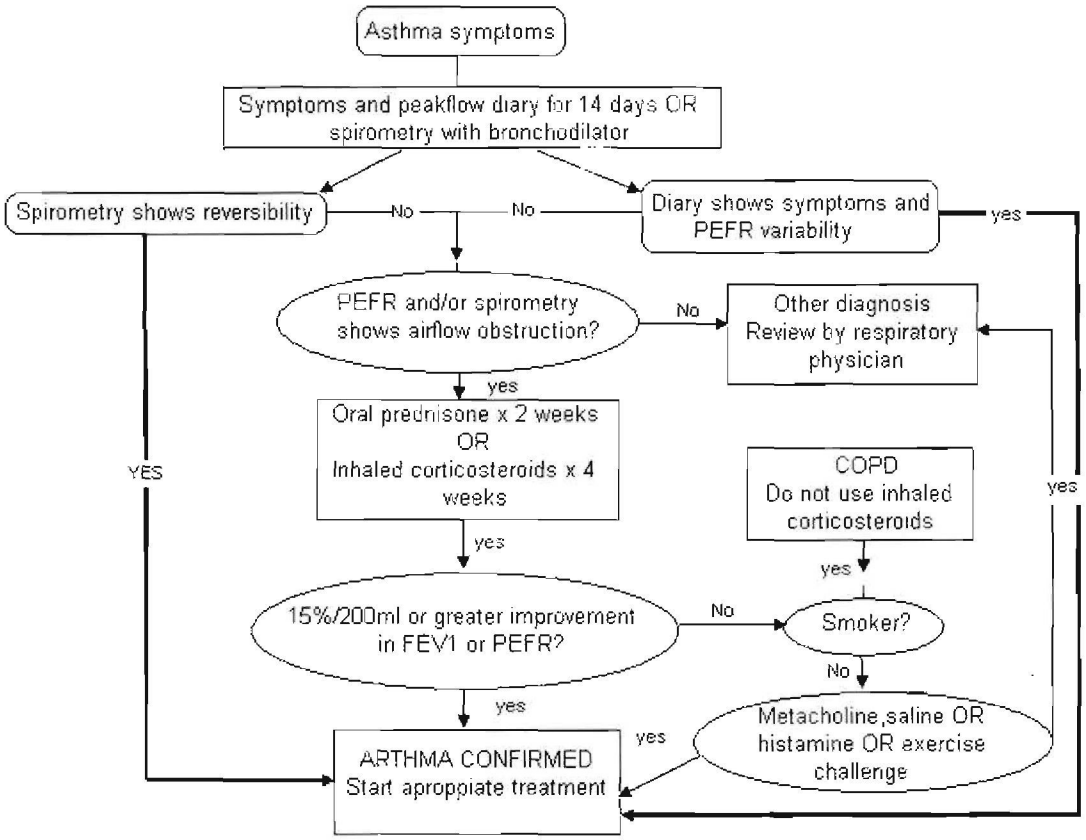
2.4 INITIAL ASSESSMENT AND DIAGNOSIS OF ASTHMA

The term asthma comes from the Greek word panting and means attack of shortness of breath. Although in the past, this term has been used for the clinical picture of shortness of breath resulting from any cause, today asthma is confined to a condition of abnormal responsiveness of the air passages to various stimuli, causing widespread airway narrowing (Wilson, 2003: 579).

According to the Current medical diagnosis and treatment (Chesnutt *et al.*, 1999: 264) asthma is defined as a chronic inflammatory condition of the airways. The histopathologic features include denudation of airway epithelium, collagen deposition beneath the basement membrane, airway oedema, mast cell activation, and inflammatory cell infiltration with neutrophils, eosinophils, and lymphocytes (especially T-lymphocytes).

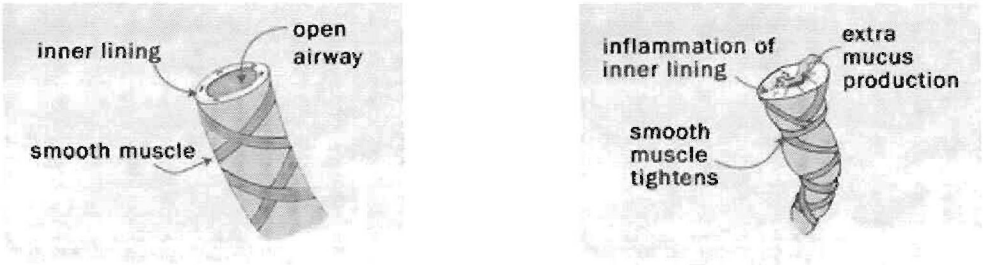
Figure 2.2 illustrates a diagnosis algorithm for asthma for accurate and effective diagnosis.

Figure 2.2 Diagnosis algorithms for asthma (Asthma and Respiratory Foundation of New Zealand, 2000).



The pathological changes as shown in figure 2.3 (see below) involved in airway destruction are found in the medium-sized bronchi and in bronchioles as small as 1mm in diameter. Airway narrowing is caused by bronchospasms, mucosal oedema and hypersecretion of viscous mucus (Wilson, 2003: 579).

Figure 2.3 Pathological changes in the bronchi during asthma attacks (Wilson, 2003: 579).



Asthma is distinguished from chronic bronchitis and emphysema by its intermittent nature and the fact that destructive emphysema rarely occurs. An asthmatic attack that continues for days and is intractable to ordinary methods of treatment (as discussed in 2.4.3) is called status asthmaticus. In these patients ventilatory functions may be so impaired as to result in cyanosis and death (Wilson, 2003: 579).

Asthma is a disorder of the tracheobronchiol tree characterised by mild to severe obstruction of the airflow. Symptoms vary, generally episodic or paroxysmal, and may be persistent. The clinical hallmark is wheezing, but cough may be the predominant symptom. It is commonly misdiagnosed as recurrent pneumonia, chronic bronchitis (Udem *et al.,* 2001: 733).

Acute symptoms are characterised by narrowing of large and small airways due to spasm of bronchial smooth muscle, oedema and inflammation of the bronchial mucosa, and production of mucus (Dambro, 1999: 98).

The four main components of airflow obstruction in asthma are (University of California San Diego, 1998):

- Acute bronchoconstriction
  Allergen-induced bronchoconstriction results from IgE dependant mediator release from mast cells. Other causes of bronchoconstriction include aspirin or non-steroid anti-inflammatory drugs (NSAIDs), exercise, cold air, irritants or stress.
- Airway oedema
  Increased micro vascular permeability due to the release of inflammatory mediators causes increased thickening and swelling of the airway.
- Chronic mucus plug formation
  In severe asthma, mucus secretion and the formation of mucus plugs can cause persistent airflow limitation.
- Airway remodelling
  Airflow limitation in some patients with asthma may be only partially reversible. This may be related to structural changes in the airway matrix, which accompany longstanding airway inflammation.

2.4.1 ASSESSMENT IN CHILDREN

Because children with asthma are often mislabelled as having bronchiolitis, bronchitis, or pneumonia, many do not receive adequate therapy (Canadian Lung Association, 2003). There is currently no specific clinical test for childhood asthma. Diagnosis is made on the basis of symptoms, such as disturbed sleep or breathing difficulties associated with coughing or wheezing (National Asthma Campaign, 2002).

The diagnosis of asthma in children involves all of the following (Canadian Lung Association, 2003):

A detailed history which would include:

- Family history of asthma, allergies, hay fever, eczema. Children will have a greater chance of developing the above if there is a family history of allergies and asthma, child's medical history including:
  - When parents first noticed the child developed breathing problems; history of nasal stuffiness (rhinitis), itchy eyes (allergic conjunctivitis) and eczema, which are common accompaniments to asthma, and hives (urticaria).
  - History of recurrent and persistent cough following a cold, frequent colds, croup, seasonal changes (i.e. worse in the spring and fall), exercise limited by breathing problems, waking at night with symptoms.
  - Number of school absences, emergency room visits (hospitalisations) because of asthma.
  - Environmental history (as discussed in section 2.5.1)

Factors associated with an increased risk of death from asthma in children include the following (University Alliance, 2005):

- Previous life-threatening episodes of asthma.
- Lack of adequate and ongoing health care. (Most likely the reason for the higher fatality rates in the minority children.)
- Significant behavioural problems.
- Underestimating the severity of an acute attack poses the greatest threat.
- Unfortunately, one study of children found that nearly 40% of them were unaware of asthmatic symptoms when they occurred

In general, forced expiratory flow (FEV_1) predicted norms or reference values used for children should also be used for adolescents (National institutes of health, 1997: 4).

Diagnosis is not needed to begin to treat wheezing associated with an upper respiratory viral infection, which is the most common precipitant of wheezing in this age group. There are two general patterns of illness in infants and children who have wheezing with acute upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. Factors associated with continuing asthma are allergies, a family history of asthma, and perinatal exposure to aeroallergens and passive smoke (National Institutes of Health, 1997: 5).

When asthma is diagnosed it can be classified as an acute or chronic condition. In acute asthma a reversible narrowing and obstruction of the airways is caused by bronchospasms and an inflammatory process triggered by allergens, viral infections, weather changes, emotional upsets or other irritants and is aggravated by mucosal oedema and viscous secretions (Department of Health, 1998: 206).

Table 2.3 indicates the additional tests for adults and children that may be necessary for the accurate diagnosis of asthma. This table displays tests to confirm a diagnosis when asthma co-exists with other conditions.

Table 2.3 Additional tests for adults and children (National Institutes of Health, 1997: 5).

Additional Tests for Adults and Children	
Additional tests may be needed when asthma is suspected but spirometry is normal, when co-existing conditions are suspected, or for other reasons.	These tests can aid diagnosis or confirm suspected contributors to asthma morbidity (e.g., allergens and irritants).
Reasons for Additional Tests	*The Tests*
• Patient has symptoms but spirometry is normal or near normal	• Assess diurnal variation of peak flow over 1 to 2 weeks • Refer to a specialist for bronchoprovocation with methacholine, histamine, or exercise; negative test may help rule out asthma.
• Suspect infection, large airway lesions, heart disease, or obstruction by foreign object	• Chest x-ray
• Suspect coexisting chronic obstructive pulmonary disease, restrictive defect, or central airway obstruction	• Additional pulmonary function studies • Diffusing capacity test
• Suspect other factors contribute to asthma (These are not diagnostic tests for asthma.)	• Allergy tests - skin or in vitro • Nasal examination • Gastroesophageal reflux assessment

The pathogenesis of chronic asthma in children is the same as in acute asthma but differs in that the inflammatory process is associated with epithelial denudation, mucosal oedema, increased and viscous secretions, and *smooth muscle contractions* (Department of Health, 1998: 210).

2.4.2 ASSESSMENT IN ADULTS

Although asthma occurs most commonly in children, it can also occur later in life. Adult-onset asthma can be associated with atopy. However, there can also be other causes of asthma. Some adults develop asthma without IgE antibodies to allergens. These adults often have coexisting sinusitis, nasal polyps and aspirin or non-steroidal anti-inflammatory drugs (NSAID) allergies (University of California San Diego, 1998). Occupational exposures to materials like plastic resins, biological enzymes, animal products and wood dusts can also cause asthma (University of California San Diego, 1998).

According to the National Guideline Clearinghouse (2003), the following information is needed to make a diagnosis:

- Medical history including family and personal history of asthma, childhood wheezing, background of atopy, hay fever, eczema or specific allergy to house dust mites, cats, pollens, food or medication. Questions regarding recent infections, exercise habits, allergen exposure, occupational exposure, medication use, smoking, stress.
- Physical examination including observation for shortness of breath with speech; wheezing and chest tightness; vital signs (e.g., respiratory rate, pulse); auscultation of chest.
- Initial testing:
    - Peak expiratory flow rate measurement.
    - Spirometry testing with bronchodilators.
- Differential diagnoses such as upper respiratory tract disease (e.g., sinusitis); post infective bronchial hyper responsiveness; chronic obstructive pulmonary disease (COPD); left ventricular failure; central airways obstruction/foreign body; vocal cord dysfunction; hyperventilation; bronchiectasis; interstitial lung disease.
- The correct assessment of severity of asthma (mild, moderate, severe) to treat the disease accordingly.
- Bronchodilator response testing or trial of oral or inhaled corticosteroids should also be noted.
- Follow-up testing should be done after diagnosis and treatment with:
    - Methacholine, histamine or saline challenge test .
    - Exercise challenge test.
    - Skin prick test.

- Referral to respiratory specialist if patient does not respond to treatment.

Table 2.4 illustrates the diagnosis for children and adults with asthma.

Table 2.4 Differential diagnosis of asthma in adults and children (University of California San Diego, 1998).

Children	Adults
• Allergic rhinitis and sinusitis • Vocal cord dysfunction • Vascular rings • Laryngotracheomalacia • Tumour or enlarged lymph nodes • Viral bronchiolitis • Cystic Fibrosis • Bronchopulmonary dysplasia • Aspiration due to gastroesophageal reflux	• Chronic obstructive pulmonary disease (COPD) • Congestive heart failure • Pulmonary embolism • Mechanical obstruction (benign or malignant tumours) • Pulmonary infiltration with eosinophilia • Cough secondary to drugs like angiotension converting enzymes inhibitors (ACE inhibitors) • Laryngeal dysfunction

Half of the children diagnosed with asthma will "outgrow" the disease during their teenage years but it usually persists if contracted in adulthood (Prakesh *et al.*, 2003).

2.4.3 ASTHMA CLASSIFICATION

Asthma is classified according to the severity, frequency and duration of symptoms, the degree to which airflow is obstructed, and the extent to which asthma symptoms interfere with daily activities (Wilson *et al.,* 2003: 578). It is important that the type of asthma the patient has is defined because treatments will differ depending on the patient's placement (American Academy of Allergy asthma and Immunology, 2002).

Pathologic asthma is divided into three categories (Wilson *et al.,* 2003: 578):

- *Extrinsic,* or allergic asthma, is found in a minority of adult patients, and is clearly caused by a known allergen. This form generally begins in childhood in a member of a family with a history of an atopic disease, including hay fever, eczema, and dermatitis, as well as asthma. Allergic asthma results from the sensitisation of the person to an allergen, usually a protein, in the

form of inhaled pollen, animal danger, mold spores, feathers, dust, lint, or, less often, to a food such as milk or chocolate.

- *Intrinsic,* or idiopathic asthma, on the other hand, is characterised by the absence of clearly defined precipitating factors. Non-specific factors such as the common cold, exercise, or emotion may trigger the asthmatic attack. (Wilson *et al.,* 2003: 578).

Most patients develop *mixed asthma*, which is composed of both extrinsic and intrinsic asthmas (Wilson *et al.,* 2003: 578). The guidelines for the diagnosis of asthma are displayed in table 2.5.

Table 2.5 Guidelines for diagnosis of asthma (American academy of allergy asthma and immunology, 2002, National asthma education and prevention, 1997: 10)

Asthma severity	Symptom severity	Night time symptoms
Severe persistent	• Continual symptoms • Limited physical activity • Frequent exacerbations interfere with normal activities	Frequent
Moderate persistent	• Daily symptoms • Exacerbations two or more times a week. These may last for days and they may interfere with activities.	More than once a week
Mild persistent	• Symptoms occur more than twice a week, but less than once a day. • Exacerbations may affect activities.	More than two times a month
Mild intermittent	• Symptoms occur two or fewer times a week. • Exacerbations are brief (a few hours to a few days) and the intensity varies.	Two or fewer times a month

Asthma is divided into different categories of severity as indicated in table 2.5 (National Asthma Council of Australia, 2004). These categories are (National Asthma Campaign, 2002);

- Mild intermittent asthma
- Mild persistent asthma
- Moderate persistent asthma
- Severe persistent asthma
- Acute severe asthmatic episode (status asthmaticus)
-

- Mild intermittent asthma

Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms (National Heart, lung and blood Institute, 2002). According to the Standard Treatment Guidelines and the Essential Drug List (Gibbon *et al.*, 2003: 44), indications for intermittent relieving therapy are, *inter alia*, the following:

- Not more than one or two episodes of daytime cough and/or wheeze per week.
- Less than one night-time cough and/or wheeze per month.
- No recent (within the last year) admission to hospital for asthma.
- Peak expiratory flow rates (PEFR) more than 80% predicted between attacks.

- Mild persistent asthma

This is defined by the occurrence of daytime symptoms more than once per week, but less than once daily, together with nocturnal awakening (due to asthma) more than once a month. Generally these interval symptoms are minor and readily responsive to bronchodilator therapy. In children old enough to perform lung function, peak flow variability is generally in the range 20 – 30% (National Asthma Council of Australia, 2004).

Table 2.6 indicates the asthma severity classification prior to the initiation of asthma therapy.

Table 2.6 Classification of asthma severity (American College of Allergy, asthma & immunology, 1997, National Asthma Education and Prevention, 1997: 10, University of California San Diego, 1998)

CLASSIFICATION OF ASTHMA SEVERITY				
	Severity prior to initiation of therapy			
	Mild Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Symptoms	< Or = 2 per week	> 2 per week	Daily symptoms	Continual symptoms
Night time symptoms	< Or = 2 per month	> 2 per month	> 1 per week	Frequent
Lung function	< Or = 80% predicted	< Or = 80% predicted	> 60% - < or = 80%	< Or = 60%
Peak flow variability	< 20%	20-30%	> 30%	> 30%

The Standard treatment guidelines and essential drug list (National Department of Health, 2003: 196), defines this category as follows:

- 2 to 4 episodes of wheeze and/or cough per week.
- 2 to 4 episodes of night-time wheeze or cough.
- PEFR more than 80% predicted between attacks.

- Moderate persistent asthma

This is defined by the occurrence of daytime symptoms more than almost daily, together with night-time symptoms more than once a week. The preferred treatment is a low to moderate dose inhaled corticosteroids plus an inhaled beta2-agonist. In patients with asthma to perform lung functions, peak flow variability will be more than 30% (National Heart, Lung, and Blood Institute, 2002)

The Standard treatment guidelines and essential drug list (National Department of Health, 2003: 196), defines this category as follows:

- More than 4 episodes of daytime wheeze, tightness or cough per week.
- More than 4 night-time awakenings per month.
- PEFR more than 60 % but less than 80% predicted.

These asthma patients should be referred when failure to control the disease occurs despite the treatment regimen (National Department of Health, 2003: 196).

- Severe persistent asthma

This class is defined by continuous daily symptoms and frequent nightly symptoms. The peak flow variability in asthma patient to perform lung function will be more than 30%. The preferred treatment is a high dose inhaled corticosteroid plus a long acting beta2-agonist **and** if needed, corticosteroid tablets or syrup for long-term use.

The Standard treatment guidelines and essential drug list (National Department of Health, 2003: 196), defines this category as follows:

- Continuous wheezing, tightness, cough.
- Frequent nocturnal symptoms.
- PEFR less than 60% predicted.

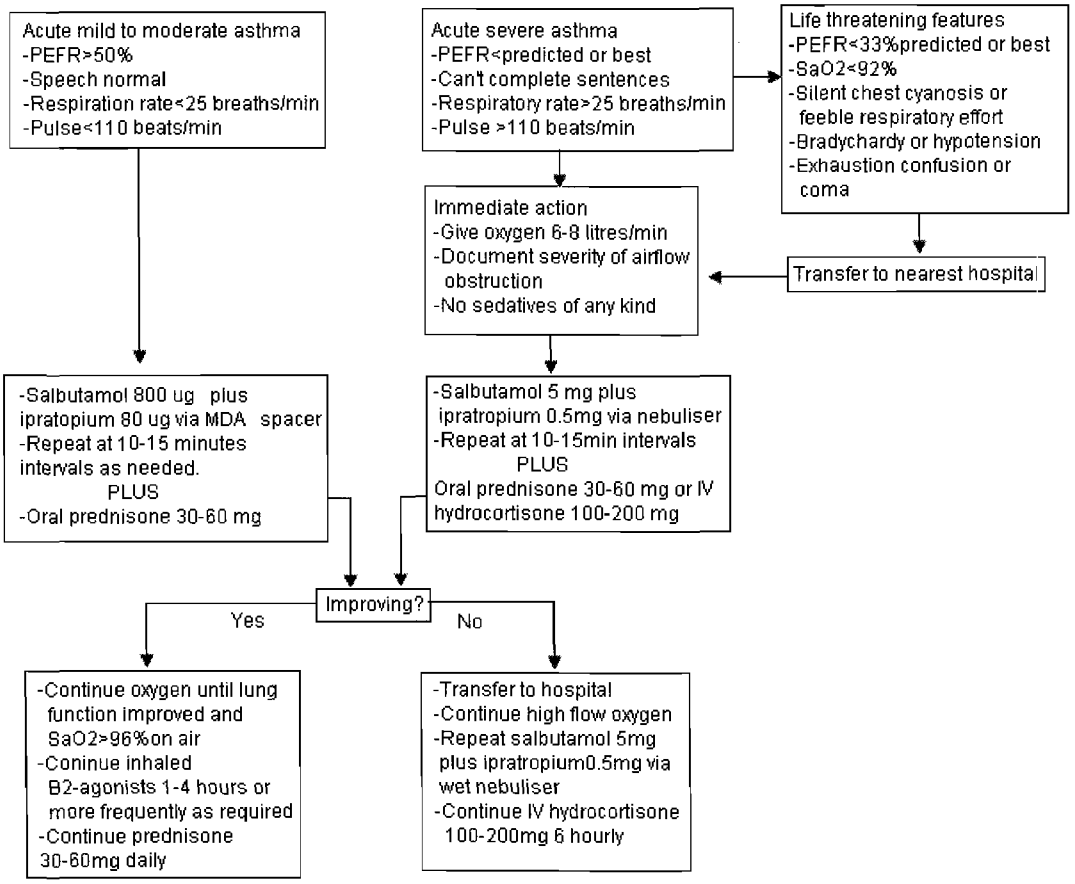
- Status asthmaticus

An asthma attack that continues for days and is intractable to ordinary methods of treatment is called status asthmaticus. In these patients, ventilatory function may be so impaired as to result in cyanosis and death (Wilson, 2003: 579).

2.4.4 ASTHMA TREATMENT ALGORITHM

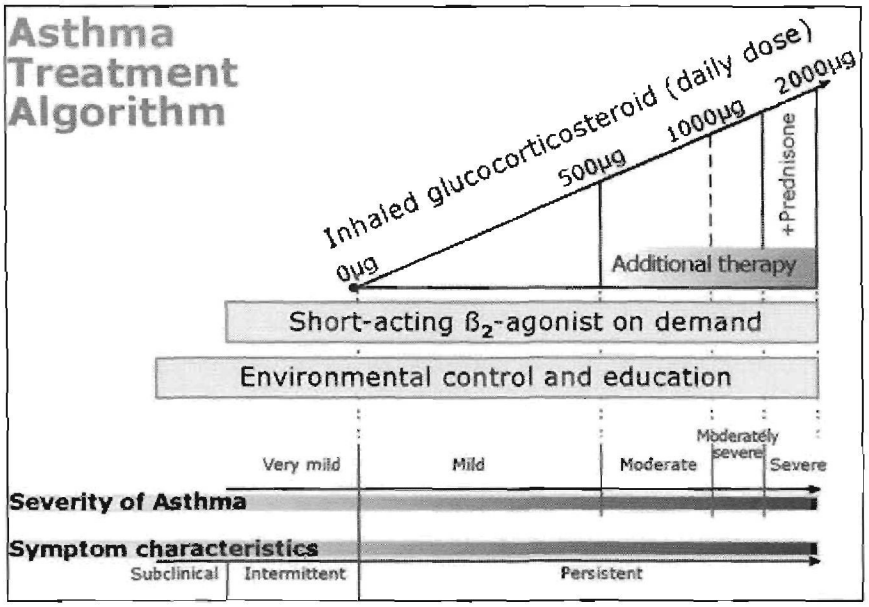
In figure 2.4 the treatment algorithm for acute asthma is illustrated. The algorithm starts with the correct diagnosis and classification of asthma as discussed in chapter 2.4.3. With the correct diagnosis the action and treatment plan for each patient is followed.

Figure 2.4 Treatment algorithms for acute asthma (Asthma and Respiratory Foundation of New Zealand, 2000).



According to the Canadian asthma consensus guidelines (2003), the asthma treatment algorithm below (figure 2.5) illustrates the timeline for the introduction of treatment as severity increases, beginning with environmental control and education at the onset of symptoms; followed by the introduction of beta agonist, inhaled steroid and prednisone therapies.

Figure 2.5 Treatment algorithms for asthma (Canadian Asthma Consensus guidelines, 2003).



The goals of long-term management of asthma should include the following (Buist, 2002):

1) Achievement and maintenance of control of symptoms
2) Prevention of asthma exacerbations
3) Maintenance of pulmonary function as close to normal levels as possible
4) Maintenance of normal activity levels, including exercise
5) Avoidance of adverse effects from asthma medications
6) Prevention of the development of irreversible airflow limitation
7) Prevention of asthma mortality

Guidelines for referral of patients to an asthma specialist:

- Patient has had life-threatening asthma exacerbation.
- Patient is not meeting the goals of asthma therapy after 3-6 months of treatment.
- Signs and symptoms are atypical, diagnosis in question.
- Other conditions complicate asthma management.
- Patient requires additional diagnostic testing, education or guidance.
- Patient is being considered for immunotherapy.
- Patient's asthma is severe persistent (or moderate persistent in children under age 3) (American College of Allergy, Asthma & Immunology, 1997).

2.5 CARE PLAN

According to the National guidelines for the diagnosis and management of asthma (National Asthma Education and Prevention Program, National Institutes of Health, 1997), asthma treatment has four main components:

- The use of objective measure of lung function (such as peak flow meters and Spiro meters) to assess the severity of asthma and to monitor the course of treatment.
- Environmental control measures to avoid or eliminate factors that trigger asthma symptoms or flare-ups.
- Medication therapy for long-term management to reverse and prevent airway inflammation as well as therapy to manage asthma flare-ups.
- Patient education to foster a partnership between the patients, his or her family, and the physician and other health care providers.

2.5.1 COUNSELLING ON TRIGGER FACTORS

Airways of people with asthma are often chronically inflamed (swollen). Therefore, the airways are sensitive to things that make asthma worse. These, either singly or together, cause symptoms in people with asthma. Identifying, controlling or treating things that make asthma worse is essential to good asthma management (National Jewish Medical and Research Centre, 2003).

Things that make asthma worse include: irritants, allergens, infections, weather, exercise, emotions, gastroesophageal reflux and hormonal changes. These vary from person to person (National Asthma Education and Prevention Program, 2003, National Institutes of Health, 1997).

- Irritants: Asthma patients should avoid exposure to environmental irritants. Environmental irritants play a major role in both childhood and adult asthma (University of California, 2003). The smoke from the burning end of a cigarette, pipe or cigar and the smoke breathed out by a smoker can trigger asthma. Other irritants include exposure to vapours, dust, gases or fumes.
- Strong odours or sprays such as perfumes, household cleaners or cooking fumes (University of California, 2003).
- Other airborne particles such as coal dust, chalk dust or talcum powder (American Academy of Allergy, 2003, Asthma and Immunology, 2003).

- Changing weather conditions (American Academy of Allergy, Asthma and Immunology, 2003).
- Infections: Viral infections such as colds or viral pneumonia can trigger or aggravate asthma, especially in young children. These infections can irritate the airways, nose, throat, lungs and sinuses, and this added irritation often triggers flare-ups. Additionally sinusitis, an inflammation of the hollow cavities found around the eyes and behind the nose, can trigger asthma (American Academy of Allergy, Asthma and Immunology, 2003, University of California, 2003, National Jewish Medical and Research Centre, 2003)
- Exercise: Exercise or physical activity makes asthma worse, for some it may be the only cause of asthma symptoms. However, exercise is important for everyone and should not be avoided (New Jewish Medical and Research Centre, 2003). Mouth breathing, exercising in cold or dry air, or prolonged strenuous activities such as medium to long distance running can increase the likelihood of exercise-induced asthma (American Academy of Allergy, Asthma and Immunology, 2003, Simon *et al.,* 2000)
- Reflux disease: Gastro oesophageal reflux disease (GERD) is a condition in which stomach acid flows back up the oesophagus and this condition can affect patients with asthma (American Academy of Allergy, Asthma and Immunology, 2003).
- Medications: Some adults may experience an asthma attack as result of taking certain medications (American Academy of Allergy, Asthma and Immunology, 2003). Adult patients should be questioned about episodes of bronchospasms after the ingestion of aspirin or other NSAIDs. If a reaction has occurred, a patient should be warned about the dangers of a fatal exacerbation with use of these drugs (U.S Environmental Protection Agency, 1999).

  Patients with severe asthma should also receive counselling regarding the potential of NSAIDs to cause a fatal exacerbation. Safe alternatives include acetaminophen and salisalate (University of California, 2003). Patients with sulphite sensitivity will have asthma symptoms after drinking beer; wine or eating processed potatoes or shrimps (University of California, 2003).

  Non-selective beta-blockers can cause bronchospasms and exacerbate asthma. Even non-selective beta-blocker ophthalmic solutions can have systemic effects and cause bronchospasms. Cardio selective beta-blockers

should be used if the use of beta-blockers is desired (U.S Environmental Protection Agency, 1999).

- Food: Some foods like milk eggs, peanuts, tree nuts; soy, wheat, fish and shellfish can cause asthma symptoms (American Academy of Allergy, Asthma and Immunology, 2003).
- Emotions: Emotions do not cause asthma, but can make asthma worse. Strong feelings can lead to changes in breathing patterns (New Jewish medical and research centre, 2003). Anxiety and nervous stress can cause fatigue, which may also increase asthma symptoms and aggravate an attack (American Academy of Allergy, Asthma and Immunology, 2003).

Dust mites are too small to be seen but are found in every home. Dust mites live in mattresses, pillows, carpets, fabric-covered furniture, bedcovers, clothes, and stuffed toys. Pets' skin flakes, urine, and saliva can be asthma triggers. Moulds grow on damp materials. The key to mold control is moisture control. If mold is a problem in your home, clean up the mold and get rid of excess water or moisture (U.S Environmental Protection Agency, 1999). Lowering the moisture also helps reduce other triggers, such as dust mites and cockroaches. Droppings or body parts of pests such as cockroaches or rodents can be asthma triggers (U.S Environmental Protection Agency, 1999).

Every person has his or her own triggers. If you have asthma you can minimise your symptoms by avoiding the factors that trigger your symptoms and by working with your physician to develop an effective management and treatment plan (National Jewish Medical and Research Center, 2003).

2.5.2 THE USAGE OF PREVENTATIVE MEDICATION

There are two main types of medicines for asthma treatment:

- Quick Relief medicines give rapid, short-term treatment and are taken when you have worsening asthma symptoms that can lead to asthma episodes or attacks. The patient will feel the effects of these medicines within minutes.

- Long-term Control medicines are taken every day, usually over long periods of time, to control chronic symptoms and to prevent asthma episodes or attacks. The patient will feel the full effects of these

medicines after taking them for a few weeks. People with persistent asthma need long-term control medicines.

Quick-relief medications that are used to provide temporary relief of symptoms include the following:

- **Bronchodilators**, generally used as "rescue medications," open up the bronchial tubes so that more air can flow through. Bronchodilators include beta-agonists and anticholinergics, and come in inhaled, tablet, liquid or injectable forms (American College of Allergy, Asthma & Immunology, 1997).

- **Corticosteroids** are administered for short-term use orally or by injection to speed up the resolution of airway inflammation (American College of Allergy, Asthma & Immunology, 1997).

Long-term control medications are taken daily to control the airway inflammation in persistent asthma. This class includes the following medication products(American College of Allergy, Asthma & Immunology, 1997) :

- **Inhaled corticosteroids:** the most effective long-term therapy available for persistent asthma. They are generally well tolerated and safe at recommended dosages (Boushey, 2001: 343, Schimmer *et al.,* 2001: 1672).
- **Cromolyn or Nedocromil**: stops the development of inflammation in the lungs, as well as helps to prevent it. Response to these two is less predictable than the response to inhaled corticosteroids. These medications are very safe (Boushey, 2001: 336, Undem *et al.,* 2001:742).
- **Leukotrienes modifiers**: to fight potent chemicals called leukotrienes responsible for airway inflammation within the body. They are generally safe (Boushey, 2001: 344).
- **Inhaled beta 2-agonists**: long acting and beneficial when added to inhaled corticosteroids (American College of Allergy, Asthma & Immunology, 1997).
- **Methylxanthines**: provide mild to moderate dilation of the airways and may have a mild anti-inflammatory effect. Theophylline is the most frequently used methylxanthine (Boushey, 2001: 337, Undem *et al.,* 2001:742).

- **Omalizumab**: approved in 2003 as a new class of therapy, known as anti-IgE, for patients with moderate to severe persistent allergic asthma. IgE is an antibody that we all have and it is responsible for causing allergic problems in some people. It may reduce allergic reactions by causing free IgE to disappear from the body so that the IgE cannot attach to pollen (and other substances that are present) (American College of Allergy, Asthma & Immunology, 1997).

Table 2.7 illustrates a list of a few active ingredients used for asthma treatment. This medicine is used for quick relief of symptoms. The important formulations are also given.

Table 2.7 Quick relief medications for asthma (Boushey, 2001: 272).

Drug	Formulations
Short-acting β_2-agonists Albuterol (Proventil®, Ventolin®)	MDI: 90 ug/puff, 200 puffs/canister
	Nebulizer solutions: 5mg/ml (0.5%)
	Dry powder (Ventolin Rotocaps): 200 ug/capsule
	Tablets: 2mg, 4mg
Albuterol HFA (Proventil® HFA)	MDI : 90 ug/puffs, 200 puffs/canister
Bitolterol (Tornalate®)	MDI : 370 ug/puff, 300 puffs/canister
	Nubulizer solution, 2 mg/ml (0.2%)
Pirbuterol (Maxair®)	MDI : 200 ug/puff , 300 puffs/canister
(Maxiar® Auto inhaler)	MDI : 200 ug/puff, 400 puffs/canister
Terbutaline (Brethaire®)	MDI : 200 ug/puff, 300 puffs/ cannister
(Brethine®, Bricanyl®)	Tablets : 2.5 mg, 5 mg
	Injection solution, 1mg/ml
Anticholinergics Ipratropium bromide	MDI : 18 ug/puff, 200 puffs/canister
	Unit dose nebulizer solution, 0.2 mg/ml (0.02%), 2.5 ml (0.5 mg)
Systemic corticosteroids Methylprednisolone	Tablets : 2, 4, 8, 16, 32 mg
Methylprednisolone sodium succinate	Intravenous injection solution vials: 40, 125, 500 mg
Prednisolone	Tablets, 5 mg
Prednisone	Tablets: 1, 2,5 5, 10, 20, 50 mg

2.5.3 COUNSELLING ON INHALER DEVICES

The pressurised metered-dose inhaler (pMDI) has traditionally been the device of choice in the delivery of drugs in the lungs. In the past 15 years, however, the range of delivery devices available has increased dramatically and pharmacists play an important role in ensuring that the most appropriate device is chosen and supplied, with accurate information on use, storage and cleaning (Botyer *et al.,* 2000: 550).

All patients should have access to and be instructed in the use of devices needed to administer medication or monitor their asthma (e.g., inhalers, spacers, nebulisers, and peak flow meters [PFMs]). Several devices may be required to ensure optimal treatment. Patients who use inhaled corticosteroids delivered by metered-dose inhalers should use a spacer to increase consistency of the dose and to minimise the possibility of local side effects. Some patients cannot easily coordinate actuation and inhalation using a metered-dose inhaler; spacers enable easier and more effective administration of medication. Spacers with facemasks and nebulisers are both available for young children (Williams *et al.,* 2003).

Inhaled therapy poses a number of challenges over and above those encountered with conventional oral therapy. Consequently, there need to be significant benefits derived from inhaling a drug rather than ingesting it in order to justify the effort required (Evarard, 2003).

For pulmonary disease, the principle benefits are (Everard, 2003):

- Speed of onset (bronchodilators).
- Improved therapeutic ratio (e.g. β-agonists, inhaled steroids);
- Ability to deliver drugs that are ineffectively absorbed from the gastrointestinal tract (e.g. cromoglycate, tobramycin, DNAse).

Table 2.8 indicates the advantages and disadvantages of the different types of inhaler devices used and prescribed.

Table 2.8 Summary of inhaler devices (Boyter *et al.*,2000: 551)

Type	Device	Advantages	Disadvantages
Aerosol	Metered dose inhaler with or without integral spacer.	Inexpensive	Difficult for patients to co-ordinate actuation and inspiration. Inefficient drug delivery as a result of poor technique.
	Breath actuated metered dose inhaler. Small volume spacer available for some devices	No requirements for co-ordination. Portable Simple to use with minimal effort	Click on actuation may be off-putting. Some devices may be expensive.
Dry powder	Turbuhaler Clickhaler Accuhaler	Simple to use with minimal inspiratory effort. Indicator of number doses remaining. Portable. Robust devices.	Devices may be expensive. Not refillable.
	Disk haler Spin haler Rota haler Aero chamber		Difficult for some patients to load or prime. Requirements to protect the capsules against extremes of temperature and humidity
Nebuliser	Compressor	Simple to use. Can deliver high doses.	Over-reliance can be a problem. Inefficient drug delivery. Steroids require a mouth piece rather than a mask. Expensive.

2.6 FOLLOW UP EVALUATION

Patients with asthma experience varying symptoms and severity because of the nature of asthma, their exposure to environmental allergens or irritants, or insufficient adherence to their medication regimen. For these reasons, they require adjustments in therapy and regular follow-up visits. The first follow-up visit should be scheduled within the month after initial diagnosis. Routine visits thereafter should be scheduled every 1-6 months, depending on the severity of asthma and the patient's ability to maintain control of symptoms (Williams *et al.*, 2003).

Routine care includes clinical assessment of airway function over time. Spirometry is recommended at the initial assessment and at least every 1-2 years after treatment has been initiated and the symptoms and peak expiratory flow have stabilised. Spirometry as a monitoring measure may be performed more frequently, if indicated, on the basis of severity of symptoms and the disease's lack of response to treatment (Williams *et al.,* 2003).

2.7 PHARMACOTHERAPY

Although asthma medication is divided into quick-relief medication and long-term control medication (as in 2.5.2), pharmacological classification is usually as follows (Undem *et al.,* 2001: 736-747).

- Corticosteroids – beclomethasone, budesonide, fluticasone.
- Short-acting B_2 agonists – salbutamol, terbutaline, fenoterol
- Long-acting B_2 agonists – formoterol, salmeterol xinofoate
- Mast cell stabilsers – sodium cromoglycate, nedocromil
- Anticholinergics – ipratropium bromied, tiotropium
- Leukotriene receptor antagonists – montelukast, zafirlukast
- Xanthines – aminophyllin, oxtrphyllin, theophyllin

Some of these drugs are used in combination for additional effects in patients where monotherapy is not efficient, for example, budesonide and formoterol, salmeterol and fluticasone, ipratropium bromied and salbutamol (Undem *et al.,* 2001: 741).

2.7.1 CORTICOSTEROIDS

Inhaled corticoids reduce airway inflammation and are very effective if used in the prophylactic management of chronic persistent asthma. They must be used regularly for maximum benefit (SAMF, 2001: 488). In severe asthmatic attacks requiring hospitalisation, aggressive treatment with parental corticosteroids is considered essential even though their onset of action is delayed for 6 to 12 hours (Schimmer *et al.,* 2001: 1672). Table 2.9 indicates corticosteroid preparations used in the treatment of asthma.

Table 2.9 Corticosteroid preparations available (Boushey, 2001: 272).

Drug	Formulations
Beclomethasone (Beclovent®, Vanceril®)	Aerosol: 42 ug/puff in 200dose container
Budesonide (Pulmicort®)	Aerosol powder: 160ug/dose
Dexamethasone (Decadron®)	Aerosol: 84 ug/puff in 170 dose container
Flunisolide (Aerobid®)	Aerosol: 250 ug/puff in 100 dose container
Fluticasone (Flovent®)	Aerosol: 44,110, and 220 ug/puff in 120 dose container; Powder: 50, 100, 250ug/activation
Mometasone (Asmanex®)	Aerosol: 200 ug/unit inhalant powder
Methylprednisolone	Tablets:2, 4, 8, 16, 32 mg
Methylprednisolone sodium succinate	Intravenous injection solution vials: 40, 125, 500 mg
Prednisolone	Tablets, 5 mg
Prednisone	Tablets: 1, 2.5 5, 10, 20, 50 mg

Glucocorticoids do not relax airway smooth muscle and thus have little effect on acute bronchoconstruction (Undem *et al.,* 2001: 738). Their effect on airway obstruction may be due in part to their potentiation of the effects of ß-receptor agonists, but their most important action is their inhibition of the lymphocytic, eosinophilic airway mucosal inflammation of asthmatic airways (Boushey, 2001: 343).

2.7.2 SHORT-ACTING B_2-AGONISTS

These drugs' mechanisms are undoubtedly to the direct relaxation of airway smooth muscle and consequent bronchodilation. These drugs are used for acute inhalation treatment of bronchospasm. The inhaled drug has an onset of 1 to 5 minutes and produces dilation that lasts for 2 to 6 hours. When given in oral dosage form the duration of action is somewhat longer (Undem *et al.,* 2001: 736). Table 2.10 indicates short-acting $ß_2$-agonists used in treatment of asthma.

Table 2.10 Short-acting $ß_2$-agonists (Boushey, 2001: 272).

Drug	Formulations
Albuterol (Proventil®, Ventolin®)	MDI : 90 ug/puff, 200 puffs/canister Nebulizer solutions: 5mg/ml (0.5%) Dry powder (Ventolin® Rotocaps): 200 ug/capsule Tablets : 2mg, 4mg
Albuterol HFA (Proventil® HFA)	MDI : 90 ug/puffs, 200 puffs/canister
Bitolterol (Tornalate®)	MDI :370 ug/puff, 300 puffs/canister Nebulizers solution, 2 mg/ml (0.2%)
Pirbuterol (Maxair®) (Maxiar® Auto inhaler)	 MDI :200 ug/puff, 300 puffs/canister MDI : 200 ug/puff, 400 puffs/canister
Terbutaline (Brethaire®)	MDI : 200 ug/puff, 300 puffs/ cannister
(Brethine®, Bricanyl®)	Tablets : 2.5 mg, 5 mg Injection solution, 1mg/ml

The $ß_2$-selective adrenoceptor agonist drugs are the most widely used sympathomimetics for the treatment of asthma at the present time. They are effective after inhaled or oral administration and have a long duration of action and significant $ß_2$ selectivity (Boushey, 2001: 340).

2.7.3 LONG-ACTING B_2 AGONISTS

These are long lasting adrenergic agonists with very high selectivity for the B_2-receptor subtype. Inhalation of these drugs gives dilation of bronchospasm of over 12 hours (Undem *et al.,* 2001: 737). Salmeterol has a delayed onset of action and is not suitable for treatment of acute exacerbations (Gibbon *et al.*, 2001: 486).

Table 2.11 Long-acting ß$_2$-agonists (Undem *et al.,* 2001: 737).

Drug	Formulations
Salmeterol (Serevent®)	Inhalant aerosol: 25 ug salmeterol base/puff in 60 and 120 dose containers Inhalant powders: 50 ug/unit
Formoterol (Oxis®, Foradil®)	Inhalant: 12ug/puff aerosol 12ug/unit inhalant powder

Long-acting drugs like salmeterol and formoterol are new generation long-acting drugs. Both drugs are potent selective ß$_2$ agonists that appear to achieve their long duration of action (12 hours or more) as a result of high lipid solubility, which permits them to dissolve in the smooth muscle cell membrane in high concentration (Boushey, 2001: 340).

Advair® and Serevent® contain the same active ingredient, salmeterol; in Serevent®, salmeterol is alone, while in Advair® it is combined with another medicine. Foradil® does not contain salmeterol; its active ingredient is formoterol. Concerns have arisen about the three drugs, the Food and Drug Administration said, because in a small number of patients they "have been associated with severe asthma exacerbations." Advair® and Serevent® already carry warnings about a study that showed a small but significant increase in deaths among people who added the drugs to their usual asthma treatment: 13 deaths in 13,176 patients who took the drugs, versus 3 in 13,179 who took placebos. Foradil® was not part of the study and does not carry such a warning (Grady, 2005).

2.7.4 MAST CELL STABILISERS

Cromlyn and Nedocromil have been reported to have a variety of activities that may relate to their therapeutic effect in asthma. They inhibit mediator release from bronchial mast cells and have the ability to reverse increased functional activation in leukocytes obtained from the blood of asthmatic patients. There have also been reports of an inhibition of leukocytes trafficking in asthmatic airways (Undem *et al.,* 2001: 742).

Table 2.12 Mast cell stabiliser preparations available (Boushey, 2001: 337).

Drug	Important formulations
Cromolyn sodium	Pulmonary aerosol (Intal): 800ug/puff in 200 dose container; 20mg/2ml for nebulization (for asthma). Nasal aerosol (Nasalcrom®):* 5.2mg/puff (for hay fever) Oral (Gastrocrom®): 100mg/5 ml concentrate (for gastrointestinal allergy)
Nedocromil sodium (Tilade®)	Pulmonary aerosol: 1.75mg/puff in a 112 metered-dose container

* OTC preparations

Cromolyn and nedocromil differ structurally but are thought to share a common mechanism of action, an alteration in the function of delayed chloride channels in the cell membrane, inhibiting cellular activation (Barnes *et al.,* 1995: 771). This action on airway nerves is thought to be responsible for nedocromil's inhibition of cough; on mast cells, for inhibition of the early response to antigen challenge; and on eosinophils, for inhibition of the inflammatory response to inhalation of allergens (Boushey, 2001: 337).

2.7.5 ANTICHOLINERGIC AGENTS

The bronchodilation produced by these drugs in asthmatic patients develops more slowly and usually more intense than that produced by adrenergic agonists. Some patients may experience a useful response lasting up to 6 hours (Bradley *et al.*, 2001: 746). A drug such as Tiotropium requires several days before optimal efficacy is achieved, and should not be used for initial treatment of acute bronchospasm (Gibbon *et al.*, 2001: 490).

Table 2.14 Anticholinergics and antimuscarinic drugs used in asthma (Undem *et al.*, 2001: 746).

Drug	Formulations
Ipratropium Bromied	MDI: 18 ug/puff, 200 puffs/canister Unit dose nebulizer solution, 0.2 mg/ml (0.02%), 2.5 ml (0.5 mg)
Ipratropium (Atrovent®)	Aerosol: 18ug/puff in 200 metered-dose inhaler; 0.02% (500ug/vial) for nebulization Nasal spray: 21, 42 ug/spray

Muscarinic antagonists competitively inhibit the effect of acetylcholine at muscarinic receptors. In the airways, acetylcholine is released from efferent endings of the vagus nerves, and muscarinic antagonists can effectively block the contraction of airway smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity (Boushey, 2001: 342).

2.7.6 LEUKOTRIENE RECEPTOR ANTAGONISTS

These drugs either act as competitive antagonists or by inhibiting the synthesis of Leukotriene (Undem *et al.*, 2001:740). The outcome of this mechanism is that they exhibit both bronchodilator and anti-inflammatory activity. They may be considered as add on additional to therapy in asthmatic patients already on inhaled steroids and might obviate an increase in steroid dose or allow a reduction in dose (Gibbon *et al.*, 2001: 492).

According to the UCDAVIS health system, leukotriene-antagonists block leukotrienes, powerful immune system factors that, in excess, produce a battery of

damaging chemicals that can cause inflammation and spasms in the airways of people with asthma (Simon *et al.,* 2000)

Table 2.14 Leukotriene Inhibitor preparations available (General Practice Airways Group, 2001).

Drug	Formulations
Montelukast (Singulair®)	Oral: 10mg tablets, chewable tablets
Zafirlukast (Accolate®)	Oral: 20mg tablets
Zieuton (Zyflo®)	Oral: 600mg tablets

Efficacy in blocking airway responses to exercise and to antigen challenge has been shown for drugs in both categories: **zileuton**, a 5-lipoxgenase inhibitor, and **zafirlukast** and **montelukast,** LTD_4-receptor antagonists (Boushey, 2001: 344).

2.7.7 XANTHENES

Several mechanisms have been proposed for the action of the methylxanthines, but none has been established as responsible for the bronchodilating effect (Boushey, 2001: 338)

The theophyllin drugs are primarily used for the relief of bronchospasm. They are responsible for the inhibition of cyclic nucleotide phosphodiesterase enzymes (PDEs). Because theophyllin relaxes the smooth muscle it can be classified as a bronchodilator, likely to contribute to the acute therapeutic efficacy in asthma (Undem *et al.,* 2001:740).

In table 2.15 methylxanthines preparations used in the treatment of asthma are shown.

Table 2.15 Methylxanthines preparations available (Boushey, 2001: 338).

Drug	Formulations
Aminophyllin (theophylline ethylenediamine, 79% theophylline)	Oral: 105mg/5ml liquid; 100, 200mg tablets Oral sustained release: 225mg tablets Rectal: 250, 500 mg suppositories Parenteral: 250mg/10ml for injection
Theophylline (generic, Elixophllin®, Slo-Phyllin® Uniphyl®, Theo-Dur®, Theo-24®, others)	Oral: 100, 125, 200, 250, 300 mg tablets; 100, 200 mg capsules; 26.7, 50mg/5ml elixirs, syrups, and solutions Oral sustained-release, 8-12 hours: 50, 60, 75, 100, 125, 130, 200, 250, 260, 300 mg capsules Oral sustained-release, 8-24 hours: 100, 200, 300, 450 mg tablets Oral sustained-release, 12 hours: 100, 125, 130, 200, 250, 260, 300 mg capsules Oral sustained-release, 12-24 hours;100, 200, 300 mg tablets Oral sustained-release, 24 hours: 100, 200, 300 mg tablets and capsules; 400, 600mg tablets Parentarel: 200, 400, 800mg/container, theophylline and 5% dextrose for injection
Dyphylline	Oral: 200, 400mg tablets; 33.3, 53.3mg/5ml elixir Parenteral: 250mg/ml for injection
Pentoxifylline (Trental®)	Oral: 400mg tablets and controlled-release tablets

2.8 ADVERSE EFFECTS OF TREATMENT AND MEDICATION

Drug therapy enables most patients to lead relatively normal lives with few adverse effects. But the heroics of these drugs carry a price tag, the more you use these drugs, the more you are subject to their side-effects (National Guidelines Clearinghouse, 2003).

In the Chest of August 2002, Sohail Kayani and Daniel Shannon determined the adverse symptomatic effects and benefits of therapy with oral corticosteroids at different doses in children with acute exacerbations of asthma. By using a questionnaire that addressed symptoms, they conducted a prospective study of the adverse effects and benefits of therapy with prednisone at two dose levels in 86 children who where 2 – 16 years of age with mild persistent asthma during an acute exacerbation. Behavioural side-effects, particularly anxiety and aggressive behaviour, were twice as common in patients receiving a higher dose level of 2mg/kg/d. Hyperactivity was another side-effect. They concluded that because the adverse side-effects were greater at high doses but the benefits comparable, that using the lower dose level of 1mg/kg/d was more beneficial in children with mild persistent asthma because of fewer side-effects.

These side-effects also have an influence on the patient's attitude towards the therapy. In a study done on inhaled corticosteroids (ICS), patients said that they had been told of some of the side-effects. Because these patients were not sure which of the side-effects associated with the ICS use was real and which were rumours. There were also concerns that health providers did not disclose harmful adverse effects. Many patients noted that their families were not supportive of chronic ICS therapy, and therefore patients needed more time to discuss concerns with the provider (Ozminkowski *et al.,* 2000:257).

Each group of drugs has its own adverse effects. These effects include the following: (National Guidelines Clearinghouse, 2003)

- Inhaled corticosteroids – Side-effects include cough, dysphonia, oral thrush, cataracts and purpura (Undem *et al.,* 2001: 739). Common side-effects of inhaled corticosteroids are throat irritations, hoarseness, and dry mouth. Rashes, wheezing, facial swelling (oedema), fungal infections (thrush) in the throat and mouth, and bruising are also possible but not common with inhalators (Simon *et al.,* 2000).

- Nedocromil – drugs have a strong safety profile and can be used in children, bronchospasms, cough, wheezing, laryngeal edema and nausea (Undem *et al.,* 2001: 742, Boushey, 2001: 336).
- Leukotriene modifiers – have shown to cause a significant increase in the half-life of warfarin. Zileuto is an inhibitor of microsomal liver enzyme CYP3A4 and can inhibit the metabolism of theophyllin, warfarin, and terfenadine (Undem *et al.,* 2001: 741, General Practice Airways Group, 2001).
- Oral corticosteroids – the side-effects of long-term steroid use include pituitary hypothalamic axis suppression, glaucoma, weight gain, acne, menstrual irregularities, insomnia, irritability, osteoporosis, growth suppression, dermal thinning, hypertension, diabetes, cataracts, muscle weakness, and Cushing's syndrome (Schimmer *et al.,* 2001: 1672, Simon *et al.,* 2000, Undem *et al.,* 2001: 740).
- Short-acting β2 agonists – effects include tachycardia, skeletal muscle tremour, hypokalamia, increased lactic acid and headache (Undem *et al.,* 2001: 737). Patients may experience fast and irregular heartbeats. People with existing heart conditions who take beta2-agonists, particularly orally or with a nebuliser, face an increased risk for sudden death from cardiac related causes (Simon *et al.,* 2000).

  Long-acting β2 agonists – tachycardia, skeletal muscle tremour, hypokalamia, prolongation of QTc interval in overdose (Undem *et al.,* 2001: 737). Nevertheless patients with diabetes, existing heart diseases, high blood pressure, hyperthyroidism and enlarged prostate, or a history of seizures should take these drugs with caution (Simon *et al.,* 2000).
- Methylxanthines – theophyllin has a narrow therapeutic index and variable metabolism so serum theophyllin levels should be closely monitored. Adverse effects at normal doses include insomnia, gastric upset, and aggravation of gastric ulcer or reflux, difficulty in urination in elderly males with prostatism. Acute toxicities include tachycardia, nausea, vomiting, tachyarrhythmia's, central nervous system stimulation, headaches, seizures hematemesis, hyperglycaemia and hypokalamia (Undem *et al.,* 2001: 745). Methylxanthines – especially theophylline – are weak diuretics. The effect may involve both increased glomerular filtration and reduced tubular sodium reabsorption (Boushey, 2001: 339).

2.9 MANAGEMENT OF ASTHMA IN PREGNANCY AND LACTATION

Uncontrolled asthma can lead to nocturnal troublesome respiratory symptoms, emergency department visits, hospitalisation, intubations and even death. Similarly, uncontrolled asthma in pregnancy can have adverse effects on both the mother and fetus (Medscape., 1999). Pregnant women with persistent asthma are at a greater risk for worsening symptoms during the course of their pregnancy than women with intermittent asthma, according to a study published in the August 2003, *Journal of Allergy and Clinical Immunology* (JACI).

A severe asthma attack can be more harmful to the fetus than asthma medication. If asthma is not treated it could cause maternal and fatal hypoxemia, which leads to complications during pregnancy and poorer birth outcomes (Mc Donald *et al.*, 1996: 485).

The achievement and maintenance of an optimal respiratory function is mandatory to avoid the chronic hypoxemia, which may be responsible for fatal distress and growth retardation. Thus, the correct and optimal management of asthma and acute exacerbations will lead to the exclusion of pharmacological treatments. The global strategy of asthma management in pregnancy includes five essential aspects (Mc Donald *et al.*, 1996: 485):

- Objective evaluation of maternal/fatal clinical conditions.
- Avoidance/control of triggering factors.
- Pharmacological treatment.
- Educational support.
- Psychological support.

Pregnant women that do need pharmacological treatment must be aided in the management of the treatment's adverse effects. Side-effects can range from a serious iatrogenic illness to minor complaints.

2.10 MANAGEMENT OF ADVERSE EFFECTS DURING TREATMENT

The medication for asthma is to relieve and prevent asthma symptoms. They are used because they are needed. As discussed in section 2.8 these medications do have side-effects with long-term use (Weinberger, 2005).

There are ways to reduce or minimise side-effects. With the use of a higher dose inhaled steroids, a spacer device should be used with the inhaler. This reduces the amount of steroid, which is absorbed into the body. It is also suggested to rinse your mouth after the use of a preventer, to make sure that any drug remains are removed from teeth and mouth (Weinberger, 2005, Simon *et al.,* 2000).

The best way to manage side-effects is to monitor the patient's asthma. Side-effects can be minimised by making sure the patient is on the lowest dose of the drug needed to keep the asthma under control (General Practice Airways Group, 2001).

2.11 BARRIERS IN THE MANAGEMENT OF ASTHMA

Patients with asthma have many barriers in the way of optimal treatment. These include a failure to recognise warning symptoms, belief in a permanent cure; not continuing treatment for as long as needed; and, an inclination to seek complimentary medicines (Singh *et al.,* 2002).

Several factors influence **asthma** care and compliance with guideline recommendations – socioeconomic issues, patient and family beliefs, and physician understanding and comfort with the guidelines.

- Socioeconomic issues

Children of lower socioeconomic class have higher rates of asthma.

- Patient and family Beliefs

Appropriate asthma management requires effective patient–physician communication about asthma therapy. Patients tend to over-report use of medication. It is estimated that 50% of patients do not use the medication as prescribed by their physician.

- Physician behaviour

Several studies demonstrate under-utilisation of NAEPP guidelines by the physicians, independent of their type of practice. Part of the reason for this is poor physician understanding of guidelines.

- Impact of education

Intense educational interventions can be effective. One study, using a combination of comprehensive asthma education (done by nurse specialist at every visit and telephonically between visits) and timely interventions facilitated by AirWatch (electronic device measuring peak expiratory flow (PEF) and forced expiratory volume in one second (FEV 1) with a central data-base collection system sent through a phone line), improved adherence to prescribed medication from 10% to 75%.

According to the National Committee for Quality Assurance (2005), prior to implementing any interventions, the plan should identify barriers through input from its advisory panel, the PCP focus group, and the member survey. Key barriers identified included the following:

- Patient noncompliance with medication regimens prescribed.
- Lack of patient understanding of the role of inhaled steroids versus beta agonists in the control of asthma.
- Failure by the patient to notify the physician of symptoms indicative of an exacerbation.
- Lack of benefit coverage for peak flow meters and spacers.
- The need for assistance with smoking cessation, particularly for parents of children with asthma.

As long as there are significant psychosocial and socio-economic factors present in a family, it is unlikely that asthma management will be a priority. A corollary to this is that asthma treatment programmes that do not address the more pressing social and economic needs of the families where asthma is present are more likely to report higher asthma exacerbation recurrence rates (Bradley *et al.*, 2001:740).

Not all barriers to care are clinical in nature. Benefit structure, contractual relationships, and authorisation systems can all have a significant impact on care. In this case, attention to these administrative barriers resulted in the identification and resolution of what had been a significant issue for members (National Committee Quality Assurance, 2005).

2.12 CHAPTER SUMMARY

Pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs, and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes. The pharmaceutical care process has three phases; the assessment, care plan, and evaluation. Asthma is a disorder of the tracheobronchiol tree characterised by mild to severe obstruction of the airflow. Symptoms vary, generally episodic or paroxysmal, and may be persistent. Asthma is classified based on the severity, frequency and duration of symptoms, the degree to which airflow is obstructed, and the extent to which asthma symptoms interfere with daily activities.

Things that make asthma worse include: irritants, allergens, infections, weather, exercise, emotions, gastroesophageal reflux and hormonal changes. These vary from person to person.

Drugs used in the treatment of asthma are:

- Corticosteroids – beclomethasone, budesonide, fluticasone.
- Short-acting B_2 agonists – salbutamol, terbutaline, fenoterol
- Long-acting B_2 agonists – formoterol, salmeterol xinofoate
- Mast cell stabilisers – sodium cromoglycate, nedocromil
- Anticholinergics – ipratropium bromied, tiotropium
- Leukotriene receptors antagonists – montelukast, zafirlukast
- Xanthines – aminophyllin, oxtrphyllin, theophyllin

Drug therapy enables most patients to lead relatively normal lives with few adverse effects. But the heroics of these drugs carry a price tag, the more you use these drugs, the more you are subject to their side-effects. Patients with asthma have many barriers in the way of optimal treatment. These include a failure to recognise warning symptoms, belief in a permanent cure; not continuing treatment for as long as needed; and an inclination to seek complimentary medicines.

In the next chapter the pharmaco-economics, pharmaco-epidemiology and the managed health care plan of asthma will be discussed.

CHAPTER 3
HEALTH CARE CONCEPT APPLIED TO ASTHMA

3.1 THE GROWING PROBLEM OF ASTHMA

There is undoubtedly evidence of a significant increase in the number of people who have asthma amongst all races in South Africa. Over the past 25 years a 25 to 200 times rise in hospital admissions for asthma has been recorded in hospitals in Durban and Soweto (Jeena *et al.,* 2004).

The steady rise in the prevalence of asthma constitutes an epidemic, which, by all indications, is continuing. Even if rates were to stabilise, asthma would continue to be a profound public health problem. The burden of this disease is felt every day, whether it is the treatment of a severe asthma attack or constant treatment plan to keep asthma under control. Appropriate medical care, monitoring of symptoms as well as other preventative factors and measures can substantially reduce the frequency and severity of asthma attacks. Still, many patients remain ill because of a complex interplay of factors (Shalala, 1998)

Even though its incidence is rising, the death rate from asthma is falling because of improved treatment; however, 1,500 people still die annually from it. Despite a better understanding and improved treatment of asthma, the prevalence, morbidity, and mortality rates have risen over the past decade. Because of the increased number of people affected, in recent years, asthma has become a major public health epidemic (Allensworth *et al.,* 2001: 8).

For decades, allergic diseases have been recognised to be infrequent amongst Africans. Consequently, recent studies have revealed a lower incidence of family history for allergy amongst them. However, if compared to other races, many more Africans who have a positive family history of allergy develop allergic diseases. The early exposure to foreign allergens from the newly adopted Western life style has contributed to the higher degree of sensitisation recorded amongst African infants, again more so than in the case of other races also exposed to the same changes in

life style. These factors account for the increased number of African children who have asthma (Jeena *et al.,* 2004).

3.1.1 THE GROWING PROBLEM OF ASTHMA IN CHILDREN

Asthma is a common chronic disease of childhood, affecting an estimated 4.4 million children. Asthma is one of the leading causes of school absenteeism, accounting for over 10 million missed school days annually. Symptoms not severe enough to require a visit to the emergency room or to a physician can still substantially impair quality of life. Asthma results in many nights of lost sleep and disruption of family and caregiver routines, and restricted activities. It is the leading work-related lung disease; and recent evidence suggests that, in some regions, as much as 20 per cent of adult onset asthma may be work related (Shalala, 1998).

In the United States, asthma affects six million children under the age of 18 with California leading the country in the prevalence of childhood asthma – 7.1% vs. a national average of 6.4%. In 2002 alone, more than 4 million of these children suffered from an asthma attack or episode. Consider these facts (Sutter Health, 2005):

- Asthma sends hundreds of thousands of children to the emergency room each year.
- Asthma is the third most common reason for children under age 15 to be hospitalised.

Taking care of asthma is expensive and imposes financial burdens on patients and their families, including lost workdays and income, as well as lost job opportunity (Science blog, 2001). In 1990, the annual cost of asthma to the U.S. economy was estimated to be $6.2 billion, with the majority of the expense attributed to medical care. A 1998 analysis using different methods estimated the cost of asthma in 1996 to be over $11 billion per year (Shalala, 1998).

The number of hospitalisations and emergency room visits for asthma has increased in all population groups. Asthma accounts for one-third of all pediatric emergency room visits and is the fourth most common cause for physician office visits. The variation in the impact of asthma across racial and ethnic groups is significant. African-American children have an annual rate of hospitalisation of 74 per 10,000,

over 3 times the rate of white children, which has been calculated as 21 per 10,000. In addition, African-American children are approximately 4 times more likely than white children to seek care at an emergency room. In short, African-American children have a slightly higher risk of getting asthma, but have a much higher risk of hospitalisation or death due to the disease (Health goods, 2004).

3.2 MANAGED HEALTH CARE PLAN

A *managed health care plan* can be defined as an arrangement that integrates financing and management with the delivery of health care services to an enrolled population. It employs (or contracts with) an organised system of providers that delivers services and frequently shares financial risk (Pam Pohly's web guide, 2005)

Managed care is a belief that a health care system should work to keep people healthy; and when they are sick or injured, should work to assure the right treatment in the right setting by the right person. At its core, it places providers at risk for the health of the community. Managed care exists in different forms, with different benefit structures, financing mechanisms, and provider configurations. It is still evolving and therefore very much a work in progress (Integrated Healthcare Association, 2005).

The fundamental components of managed care plans are described; the development of managed care programmess is discussed; and the impact of managed care on pharmacy services and the price, quality, and accessibility of health care are reviewed. Health care can be considered to be managed when at least one of the following fundamental components is present: prospective pricing, "UCR" (usual, customary, and reasonable) pricing of services, peer review, mandatory use review, benefit redesign, capitation payments, channelling, quality criteria, and health promotion (Curtiss, 1989: 742).

The principles of managed health care are defined as listed below (Integrated Healthcare Association, 2005):

- Managed care organisations should encourage access to health coverage - including those with greatest health risk.

- Managed care organisations must recognise physicians' preeminent role in making medical decisions and must endeavour to ensure strong physician leadership.
- Managed care organisations should promote members' health by ensuring that health plans and providers are incentivised to provide high quality medical care.
- Managed care organisations should be accountable for the health of members by preventing as well as managing diseases and illnesses.
- Managed care organisations are ultimately accountable for their members' health, and for the outcomes of the treatment members receive.
- Managed care organisations should communicate the outcomes of their services, based on valid measures of medical quality.
- To fulfil their responsibility to society and the communities they serve, managed care organisations should collaborate with public sector agencies to resolve gaps between commercial insurance and safety net programmes.
- Managed care organisations can help government fulfil its responsibility to ensure health care for all through the provision of a more cost-effective and comprehensive system of care.

3.3 DRUG UTILISATION REVIEW

Drug utilisation review (DUR) is a process conducted through the pharmacy at the point of sale at time of dispensing. For each different prescription, drugs are checked against a series of criteria, based on the plan member's medical drug history, to ensure that he or she is not taking drugs inappropriately (Health Assure, 2003). Drug utilisation review helps pharmacists fulfil their professional responsibility and ensure that medication is dispensed safely and also assists in monitoring compliance to the physician's intended drug regimen (Health Assure, 2003).

According to Emergis (2003) the DUR pays attention to the following:

- Drug interaction – to look for other known medicinal ingredients that may interact adversely with ingredients in the current medication.
- Therapeutic duplication - to make certain whether the current medication contains ingredients in the same therapeutic class as historically claimed

previous medication that may still be active in the patient's body. This could cause a drug concentration higher than the physician intended.

- Refill too soon/Too late – to indicate whether a drug prescription is being refilled too early or too late, providing indication of potential non-compliance.
- Minimum/Maximum Dosage – to determine whether the daily dosage of the current medication falls within the prescribed age band dosage limits as established by the drug manufacturer.
- Drug gender – to alert the pharmacist to specific gender-related indications, the gender the medicine is intended for if applicable.
- Drug age – to establish whether the product may be harmful to a patient who is a child or a senior.

Drug utilisation review can be defined as a method for evaluating or reviewing the use of drugs in order to determine the appropriateness of the drug therapy (Arnold, 2005). According to Pharmapath's Glossary of Drug Benefits Terms (2003), drug utilisation review is defined as a complex managed care process that occurs as part of the reimbursement process. A review conducted before the drug is dispensed by the pharmacy or administered by the physician is a pre-authorisation review. A review conducted afterwards is a retrospective review. A failure to pass either type of review will result in a failure to secure drug reimbursement. Some aspects of drug utilisation review are designed to protect patients from dangerous reactions to medications. For example, one aspect of the review process seeks to protect patients from drug-to-drug interactions. Other aspects seek to make sure that doctors follow specific prescribing guidelines for specific diseases. The drug utilisation review process can also be used as a way for health plans to avoid - or at least delay - having to pay for an expensive drug a doctor wants to use or prescribe. When doctors and patients have access to the right information, they can work most effectively with health plans on a level playing-field - applying the advantages of drug utilisation review to the benefit of everybody.

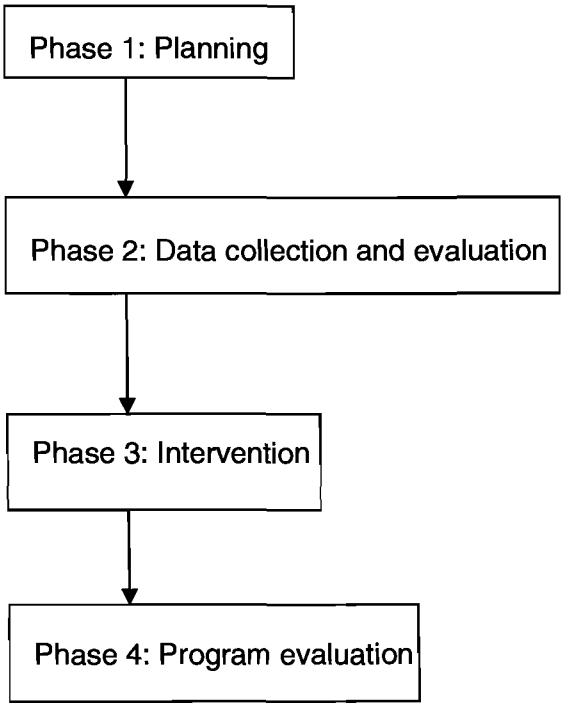
A DUR programme is any programme operated solely or partially as a professional standards review organisation whose purpose is to educate pharmacists and practitioners on severe adverse reactions to drugs, therapeutic appropriateness, over utilisation and underutilisation, appropriate use of generic products, therapeutic duplication, drug-disease contraindications, drug-drug interactions, incorrect drug dosage or duration of drug treatment, drug-allergy interactions and clinical abuse or

misuse, as well as to identify and reduce the frequency of patterns of potential and actual fraud, abuse, gross overuse, inappropriate care or medically unnecessary care associated with specific drugs or groups of drugs among practitioners, pharmacists and patients (Legislative Research Council of South Dakota, 2004).

A DUR board can be defined as follows: Acting in an advisory capacity, The Board assists in the development of clinical guidelines to be used in the DUR Programme. Meeting quarterly, the Board is comprised of a minimum of twelve members: represented by physicians and pharmacists of various specialties of the medical community (University of Massachusetts, 2005)

Drug utilisation evaluation is an effective mechanism to identify individual variability in drug use and to promote interventions that will improve patient outcomes (Stempel *et al.,* 1996: 153*).*

According to Moore *et al.* (1997), developing a DUR programme consists of 4 phases.



The DUR process is flexible and broadly applicable and can be used to assess the quality and economy of drug prescribing, drug use by patients and drug dispensing. Moore *et al.* (1997) state that this review can be divided into general steps:

- Form a DUR Committee.
- Write policies and procedures
- Define all areas or departments where drugs are used (e.g., emergency room, intensive care unit, radiology, surgical department, medical department).
- Identify drugs for possible inclusions in the programme.
- Assess resources available for criteria development, data collection, and evaluation, and choose drugs to be included in programme.
- For each drug, select aspects (indications, dosing, dosage form chosen, etc.) of drug use to monitor and evaluate.
- Select criteria and establish performance thresholds.
- Establishing methodology for data collection and evaluation and create a schedule.
- Educate staff about DUR programme and current criteria.
- Collect data.
- Evaluate data and determine whether drug use problems exist.
- Disseminate results to staff.
- If a drug use problem was found, design and implement interventions.
- Disseminate results of re-evaluation.
- Evaluate all DUR programme activities at end of the evaluation year, and plan programme activities for the next year.

3.3.1 PROSPECTIVE DRUG UTILISATION REVIEW

Prospective drug utilisation review (DUR) involves comparing drug orders with criteria before the patient receives the drug. This type of evaluation is ideal for its preventive potential, and for individual patient-centred interventions (Moore *et al.*, 1997:2).

According to the Massachusetts Division of Medical Assistance (2004) and their drug utilisation review programme prospective DUR entails the following: Prior to dispensing prescription medication, the pharmacist is required to screen for possible drug therapy problems including incorrect dosing, over/under-utilisation, drug-drug interactions, drug-disease interactions, duplicate therapy, and possible abuse. Another definition for this programme includes that it addresses specific topics through newsletters, academic detailing, and promotions to physicians and pharmacies. It is audience-specific and educational. The programme is designed to support patient consultation by pharmacists and physicians (Principle Financial Group, 2001).

3.3.2 RETROSPECTIVE DUR

Retrospective DUR involves reviewing drug prescribing and use after they have occurred. Although this is the easiest and least costly approach, with retrospective DUR there is no opportunity to modify therapy for the patients whose data were collected (Moore *et al.*, 1997:2).

Retrospective drug utilisation review manages prescription drug use by reviewing prescribing and dispensing patterns. All claims are reviewed according to established utilisation profiles for patients, pharmacies, and physicians. Beyond patient-specific issues, physician and pharmacy profiles are compared to those of their peers and to national norms to identify significant differences (Principle Financial Group, 2001).

Retrospective DUR entails that the programme occurs after the prescription has been dispensed and targets patterns involving the prescribers, pharmacists, and Medicaid recipients. Under guidelines of the DUR Board, educational interventions are executed to promote proper use of prescription medicines. Such interventions include providing educational material to pharmacists, providers, and recipients (Massachusetts Division of Medical Assistance, 2003).

Table 3.1 compares a retrospective DUR with a prospective DUR.

Table 3.1 Prospective vs. Retrospective (Wisconsin Medicaid Pharmacy Handbook, 2001)

Prospective DUR	Retrospective DUR
• Performed before a drug is dispensed. • Identifies a potential problem before it occurs. • Provides real-time response to a potential problem. • Has preventive/corrective action	• Performed after a drug has been dispensed. • Warns when a potential problem has occurred. • Useful for detecting patterns. • Useful for designing targets for intervention. • Has corrective action

Retrospective drug utilisation review is required of all State Medicaid Programmes and is performed by most private sector prescription programmes in America. However, it has not been shown to improve clinical outcomes or reduce the rate of potential prescribing errors, known as "exceptions" (Hennessy *et al.,* 2003).

3.3.3 CONCURRENT DUR

Concurrent DUR involves reviewing drug orders during the course of therapy. This type of evaluation is ideal where adjustments to drug therapy may be necessary based on ongoing diagnostic and laboratory tests (Moore *et al.*, 1997:2).

Concurrent drug utilisation review processes and communicates real-time alerts, warnings and/or benefit denials to network pharmacies. This provides pharmacists with the information needed to coordinate each patient's complete drug therapy during the dispensing process. The system screens each prescription for several possible complications, including drug interaction, therapeutic duplications, excessive or insufficient doses, and excessive utilisation. It helps prevent unnecessary or inappropriate dispensing of drugs at the point of sale (Principle Financial Group, 2001).

3.3.4 DRUG UTILISATION REVIEW REQUIREMENTS

The Omnibus Budget Reconciliation Act (OBRA) of 1990 requires that all State medical assistance programmes in America include a retrospective and prospective drug utilisation review (DUR) programme for all covered outpatient pharmaceuticals as well as patient counselling (South Dakota Department of Social Services, 2004).

The primary goal of drug utilisation review is to enhance and improve the quality of pharmaceutical care and patient outcomes by encouraging optimal drug use. The DUR programme must ensure that prescribed medications are appropriate, medically necessary, and are not likely to result in adverse medical outcomes. The DUR programme includes: retrospective DUR, prospective DUR, and the State DUR Board, as well as patient counselling (South Dakota Department of Social Services, 2004).

3.3.5 TRADITIONAL DRUG UTILISATION REVIEW

Moving traditional retrospective DUR toward disease management will involve consideration of health outcomes and pharmaco-economic findings. Although definitions of disease management may vary, the common theme is the creation of population-based, integrated approaches to the provision of ongoing, cost-effective, and clinically efficacious care (Hennessy *et al.,* 2003). Disease management has been defined in one model to contain at least four essential components: coordination of care across the health care delivery system, a comprehensive knowledge base for treatment of the disease (from primary prevention through palliation), integrated information systems, and continuous quality improvement methods. Few disease management programmes currently meet all of these criteria (Moore *et al.*, 1997:4).

However, traditional DUR combined with elements of disease management expands the DUR focus from only drug-specific problems to an approach that also uses treatment guidelines and algorithms to evaluate the appropriateness of drug therapy in the context of treating particular diseases. Within this broader context, outcomes research and pharmaco-economics have important roles to play in the selection, development, and evaluation of retrospective DUR/disease management

programmes (South Dakota Department of Social Services, 2004). In some MCOs, medical and pharmacy directors' efforts have moved away from traditional retrospective DUR toward a broader treatment guideline/health outcomes-driven approach to retrospective DUR/disease management. This methodology uses retrospective DUR strategies by determining the historic compliance rate with established treatment guidelines. However, to influence how medications are to be used in the future, it also incorporates concurrent/prospective DUR strategies by promoting educational outreach efforts to provide treatment guidelines and monitoring strategies (Hennessy *et al.,* 2003).

3.4 PHARMACO-EPIDEMIOLOGY APPLICABLE TO ASTHMA TREATMENT

Epidemiology is the study of how often diseases occur in different groups of people and why. Epidemiological information is used to plan and evaluate strategies to prevent illness and as a guide to the management of patients in whom disease has already developed. Like the clinical findings and pathology, the epidemiology of a disease is an integral part of its basic description (BMJ, 1997).
Pharmaco-epidemiology can be defined as the study of the use and the effects of drugs in large groups of people. It can be viewed as an epidemiological discipline with particular focus on drugs (Hallas. 2001: 7).

Types of pharmaco-epidemiologic investigations involve the evaluation of aspects such as the following (Andrade *et al.,* 2000: 1):

- Adverse and beneficial drug effects.
- Medication utilisation patterns.
- Drug effects on quality of life.
- Economic impact of medicine use.

Pharmaco-epidemiology is becoming increasingly important with the aging of western populations, due to the increased prevalence of medication use among older people. In such patients, the evaluation of adverse consequences of using multiple medications concomitantly is particularly important (Andrade *et al.,* 2000: 1).

The term is derived from the word "epidemic", a word used by Hippocrates when describing a disease visiting the people. Modern use of the term retains the restriction to human populations, but has broadened the scope to include any type of disease, including those that are far from transient. Thus epidemiologists study chronic diseases, such as asthma, as well as such infectious diseases as cholera that might be inferred from the idea of an "epidemic" (Woodward, 1999: 1).

Pharmaco-epidemiological methods are increasingly being used to evaluate the total costs associated with drug therapy. These studies include evaluations of the total effect of dugs on utilisation of medical services and costs of total medical care. The rates and costs of beneficial and adverse drug effects may be quantified, including resource costs such as medication acquisition and administration, inpatient and outpatient visits, laboratory tests and procedures, transportation to medical care facilities, and pain and suffering of the patient (Andrade *et al.*, 2000: 4).

Such alternatives may be used to compare the cost effectiveness of two or more alternative therapies which have different ingredient costs and differ in efficacy. Studies evaluating the additional resource utilisation associated with adverse drug events in hospitalised patients have assessed the costs of longer periods of hospital stay (Andrade *et al.*, 2000: 5).

3.5 PHARMACO-ECONOMICS

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

3.5.1 DEFINING PHARMACO-ECONOMICS

Economics is about trade offs and choices between wants, needs, and scarcity of resources to fulfil these wants. Pharmaco-economics has been defined as the description and analysis of the costs of drug therapy to health care systems and society (Townsend, 1987: 134). It can also be described as the application of economic evaluation methods to drug products and pharmacist services (Vogenberg, 2001: 4).

Pharmaco-economic research identifies, measures and compares the costs (i.e., resources consumed) and consequences (clinical, economic and humanistic) of pharmaceutical products and services (Townsend *et al.*, 1996: 7).
The earliest definitions of Pharmaco-economics were very narrowly focused on the analysis of costs of the drug therapy to health care systems and society. But recently a much broader view of pharmaco-economics involves assessing the implications of projected outcomes and costs of pharmaceutical products for decision making -- whether to continue or to stop development of a drug and for global pricing strategy (Nagappa *et al.*, 2002).

3.5.2 THE IMPORTANCE OF PHARMACO-ECONOMICS

The importance of pharmaco-economic information to health care decision makers will depend upon the viewpoint from which the analysis is conducted (i.e., including only costs that are relevant to managed care).

The demand for pharmaco-economic analyses conducted by pharmaceutical firms is likely to grow substantially in the near future as managed care providers, pharmacy benefit managers, and foreign pricing and reimbursement authorities increasingly demand credible evidence of pharmaceutical value.
These market pressures, together with high drug development costs, argue strongly for early economic evaluation to guide the initial selection of candidate compounds and their development, to ensure that appropriate data are collected for late-stage cost-effectiveness studies, and to inform early termination decisions for uneconomical candidates (DiMasi *et al.*, 2001).

Health economic studies are becoming more widely available, and whilst it is unlikely that clinicians will make decisions based solely upon such analyses, such data may increasingly aid clinical choices (Jones, 2005).

In the management of asthma, clinical decision making is primarily directed toward achieving the best outcome for the patient. However, the interest of the provider, insurer, and employer must also be taken into account. An integral part of this process is an understanding of the need to weigh therapeutic objectives against economic concerns. This process involves the consideration of the potential for clinical benefits as opposed to adverse treatment effects, as well as direct and

indirect costs. Data from clinical trials provide the foundations for evaluating these factors. Randomised clinical trials, post-marketing studies, surveillance programmes, and observational claims analyses all contribute valuable information to facilitate this process (Stempel *et al.,* 2002: S503).

The aim of pharmaco-economics is to ensure the most efficient use of limited resources. On the whole pharmaco-economics should be thought of as a dynamic ongoing process, which communicates between research and development and marketing departments of the pharmaceutical industry. However, with its continued interventions, it helps in the metamorphosis of the structure of the industry toward an efficient use with sustenance (Nagappa *et al.*, 2002).

The ultimate aim of pharmaco-economics is to assist the decision makers in achieving allocation efficiency in the health care system. This is in response to the increased need for accountability during the age of cost-containment in health care (Chuen, 2003: 192). According to Nagappa *et al.* (2002) the basic idea behind pharmaco-economic evaluation of a health programme is relatively simple as it seeks to identify measures and values, their cause and outcomes simultaneously. The ultimate aim of pharmaco-economic evaluation is to provide a menu of choice for decision making regarding the allocation of resources between different programmes. To this at least two alternatives need to be considered at a time, as there are potential conflicts of interests between different segments of the populations and/or majority of the population vs. minority (Nagappa, 2002).

The objective of pharmaco-economic evaluation is to provide evidence-based information to be used in reimbursement decisions, but will not replace the reimbursement decision. A pharmaco-economic evaluation allows for determining whether a given product has additional economical benefit (superior to existing alternatives) that would justify a reimbursement or change the level of existing reimbursement status. Argumentation rising from this evaluation is important; however, it is not the only element in the complex decision-making process (Orlewska *et al.*, 2001).

The objective of pharmaco-economic analysis is to improve public health through better decision making and to determine relative values of alternative therapies (White, 2001).

The role of pharmaco-economics expanded by including the assessment of the implications of projected outcomes and products to decide whether to continue or stop drug development and also to assist in global pricing strategies (Nagappa *et al.*, 2002)

An effective pharmaco-economic approach to formulary development emphasises high-cost (cardiovascular and gastrointestinal disorders, depression, diabetes), high-utilisation (migraine, asthma, allergy, and metabolic disorders), and high-impact (AIDS, cancer, organ transplant) medications. A plan may also endeavour to consider pharmaco-economics where there are significant variations in usage patterns (White, 2001).

Pharmaco-economic analysis can be performed on all pharmaceutical products for which an application for reimbursement is submitted, except in the following cases:

- Pharmaceutical products with the same active ingredient as in a pharmaceutical product for which reimbursement has already been granted, including generic pharmaceuticals, parallel-imported preparations and preparations in new packaging

- Pharmaceutical products for which a new formulation quite clearly does not change the costs and health effects of treatment (Orlewska *et al.*, 2001).

Pharmaco-economic analysis is especially useful for decision making, concerning pharmaceutical products with earlier not reimbursed indications or belonging to a new therapeutic class of products, which were earlier not reimbursed (Orlewska *et al.*, 2001).

Pharmaco-economic evaluation, *i.e.* economical analysis, of pharmaceutical products is a method, which in a clear and precise way defines "added value " that the product contributes to the health of society. The overall objective of pharmaco-economic analysis is to provide reliable information that can support the decision-making process in order to achieve efficiency in resource allocation. Pharmaco-economic analysis aids the decision-making process in terms of enhancing the information on which decisions are based, allows decision makers to make informed choices based on evidence, and contributes to an efficient resource allocation (Orlewska *et al.*, 2001).

It is, therefore, evident that it would be necessary to elaborate on certain guidelines along which to conduct pharmaco-economic evaluations. (Orlewska *et al.*, 2001). Such guidelines would, *inter alia*, consider the following matters:

- Objective - use of pharmaco-economic evaluations and their status (compulsory or voluntary).
- Methodology followed in pharmaco-economic evaluations.
- Ethical principles while conducting pharmaco-economic evaluation and when making the same publicly known.

Most pharmaco-economic analyses are of the cost-effectiveness type, designed to ask: "Which treatment is more effective?" The simplest form of analysis is to calculate a mean cost-effectiveness ratio that gives an indication of the average cost of achieving a given outcome with each treatment (Jones, 2005).

2.5.3 METHODOLOGY FOLLOWED IN PHARMACO-ECONOMIC EVALUATIONS

Pharmaco-economic evaluations primarily consider the costs and consequences of a pharmacologic intervention and are often applied among various alternatives (Venturini *et al.*, 2002: 8).

Each health care problem to be addressed by pharmaco-economic evaluation, should be carefully defined. The problem must be worded in such a way that the issues to be addressed are revealed. In order for the analysis to appear credible and transparent, its assumptions, parameters and limitations must be clearly stated (Orlewska *et al.*, 2001).

The method chosen depends on the nature of the comparison being undertaken, and on the way in which benefits are measured (Orlewska *et al.*, 2001):

- Cost-minimisation analysis (CMA)
- Cost-effectiveness analysis (CEA)
- Cost-utility analysis (CUA)
- Cost-benefit analysis (CBA)
- Cost-of-illness analysis (COI)

- Cost-consequences analysis (CCA)

These methods are defined and discussed more completely in section 3.5.5.
The analysis must contain a description of the illness for which the pharmaceutical product in question is to be used and a profile of the patient group(s) who is/are the target group(s) for the drug. The anticipated number of patients who will use the new drug should be estimated (prevalence and incidence figures). Estimates should also be made of discontinuation and death among patients. If the drug is regarded as being more cost-effective for a narrower patients group than the one covered by the indication, this should be specified (Orlewska *et al.*, 2001).

Within health economics a variety of questions should be considered, e.g.: the financing of health care; the behaviour of providers and patients and the incentives provided to them by the health care system; the production and cost of health care, including new technologies.
Due to the increasing shortage of funds, however, health economics methodology is increasingly used to evaluate different treatment options regarding their efficiency. Results of an economic evaluation, e.g. a cost-effectiveness analysis of a treatment compared to an alternative, are used to provide information to all decision makers involved, pertaining to coverage and reimbursement (Eucomed, 2005).

It is therefore not the objective of health economics methodology to provide recommendations how to merely cut costs, but rather how to optimally allocate the existing resources within a health care system (Eucomed, 2005).

The methodology used (CMA, CEA, CUA, CBA) needs to be stated and established. Indiscriminate use of pharmaco-economic terminology has been documented in medical and pharmacy literature and inappropriate terms are often utilised. The chosen method needs to be appropriate for the problem under study. If the two treatment alternatives show a substantially overlapping efficacy-effectiveness and safety profile, the most appropriate methodology is CMA. Otherwise, in evaluating a pharmacological treatment that substantially improves quality of life, the choice of CUA would be more appropriate than CEA (Venturini *et al.*, 2002: 9).

3.5.4 ETHICAL CODE OF PRACTICE OF PHARMACO-ECONOMIC ANALYSIS

Scientific institutions, independent experts and representatives of pharmaceutical industry can conduct pharmaco-economic studies. It is important that personnel conducting above studies dispose of relevant skills to conduct them (knowledge of methodology, high professional ethics). Analysis should be conducted in accordance with methodology guidelines. It should be clear what relationship is present between the executing partner and order provider. Above all, this will be critical for freedom of publication to follow (Orlewska *et al.*, 2001).

3.5.5 ECONOMIC EVALUATION METHODS

Pharmaceutical companies have carried out most pharmaco-economic analyses in asthma, so it is not surprising that where comprehensive data are published, they usually favour the products produced by that company. One company, in particular, has a very productive health economic department with many papers in the asthma therapeutic field. In most cases comparisons of differences in cost-effectiveness of similar classes of agents produced by different companies are relatively small (Jones, 2005).

There are several pharmaco-economic evaluation methods. These methods will be discussed subsequently.

3.5.5.1 Cost-minimisation analysis (CMA)

Where the benefits of the interventions are identical, e.g. comparing the costs of a generic drug and branded drug provided they are bioequivalent (National Prescribing Centre, 2000: 3).

Very frequently, however, CMA is confused with COI, but they are substantially different in scope and methodology. In reality, it is very difficult to find a situation for a true equality in efficacy/effectiveness and safety so this method is rarely applicable. The ideal situation for a CMA is the comparison of a brand and equivalent generic drug (Venturini *et al.*, 2002: 11). According to the Norwegian Medicines Agency

(2004) the condition of identical health outcomes for different treatment programmes is seldom fulfilled, but the method is recommended in cases where this occurs.

3.5.5.2 Cost-effectiveness analysis (CEA)

Where the benefits are common, unidimensional and measured in the same natural units, e.g. comparing the number of deaths prevented by coronary artery bypass with the number prevented by use of a statin (National prescribing centre, 2000: 3).

$$CER = \frac{(\cos t.of\ .treatment.A) - (\cos t.of\ .treatment.B)}{(clinical.success.treatment.A) - (clinical.success.treatment.B)}$$

There has been much discussion regarding the use of "efficacy" or "effectiveness" for computing the CER in CEA. **Efficacy** can be defined as performance of a treatment under ideal and controlled circumstances (Venturini *et al.,* 2002:8). Efficacy studies pay strict attention to internal validity (the accuracy of the conclusion) at the expense of external validity (ability to generalise results to the real world clinical practice setting). An example of an efficacy study is a clinical trial (Venturini *et al.,* 2002: 7).

Cost-effectiveness analyses can be used when the treatment programmes to be compared give the same type of health outcome, e.g. two drugs which reduce the number of asthma attacks. In such a case the health outcomes can be compared (de Lissovoy *et al.,* 2002). The method cannot be used when one wants to compare the value of different treatment programmes that have different forms of health outcomes, such as treatment of gastric ulcers vs. treatment of migraines (Norwegian Medicines Agency, 2004).

Cost-effectiveness analysis is more interpretable when the "effect" is defined in more universal terms such as incremental cost per life-year saved (de Lissovoy *et al.,* 2002).

3.5.5.3 Cost-utility analysis (CUA)

The cost-utility method is well established. The advantage is that in principle the method makes it possible to compare the value of scanty resource funding for entirely different, competing applications (Norwegian Medicines Agency, 2004).

The benefits of this analysis are multidimensional, and include measurement of both quantity and quality of life, e.g. comparing the number of quality-adjusted life-years (QALYs) gained by use of an anti-asthmatics with those gained by a hip replacement (National Prescribing Centre, 2000: 3).

Technically speaking there are two reasons why the QALY-calculations can be misleading as a basis for decisions involving societal priority setting. One is that the life quality scores (on a zero-one scale) attributed to different health problems are often too low (de Lissovoy *et al.,* 2002). The consequence of this is that programmes for moderate health problems are given far too great an emphasis in the analysis compared to programmes for serious health problems, and symptom alleviation and functional improvement are generally given too great a value compared to life-saving measures. The second reason is that the QALY-approach places an excessive importance on the number of years for which patients will benefit from a treatment. This can lead to the value of treatment programmes for elderly patients being set too low compared to the value of treatment programmes for younger patients (Norwegian Medicines Agency, 2004).

3.5.5.4 Cost-benefit analysis (CBA)

The benefits of this analysis are valued in monetary units, e.g. comparing the amount of money one is willing to pay to prevent a death by either instituting a breast screening programme or a cervical screening programme (National Prescribing Centre, 2000: 3).

Patient benefit of a treatment programme (such as improved quality of life and/or prolonged lifetime) is quantified in cost-benefit analyses in NOK (Norwegian krone) instead of in physical units or QALYs. Quantification is usually based on hypothetical questions to the population about what they would be willing to pay for different types of health improvement, if they lived in a system where they had to pay for improvements directly from their own pocket (the payment willingness principle). Cost-benefit analyses are used relatively seldom as pharmaco-economic analysis, because there is great uncertainty concerning the validity of measurements of hypothetical willingness to pay for health services (Norwegian Medicines Agency, 2004).

The aim of cost benefit analysis (CBA) is to construct cost or outcome ratios (average and incremental) to compare the alternative regimen. To compare the different outcomes (positive or negative) a common denominator is needed which is stable, plausible, and consistent and incorporates most possible outcomes. In cost benefit analysis the common denominator for conversion is currency. The positive and negative consequences of the medical interventions are expressed in terms of currency and aggregates (Nagappa *et al.*, 2002).

3.5.5.5 Cost-of-illness analysis (COI)

This analysis shows the cost of the condition in question to society over a specific period of time. A CAO is a pure cost analysis and health consequences are not evaluated. The total cost is calculated, but not the incremental cost (Orlewska *et al.*, 2001). The terms marginal cost and incremental cost are often used interchangeably in published economic evaluations. However, marginal cost is more often used to reflect the extra costs of producing one more unit of output within a programme (for example, an extra operation) whereas incremental cost tends to be used to reflect the difference in costs between different programmes (for example, between types of operation) (National Prescribing Centre, 2000: 3).

Cost of illness studies is a type of economic study common in the medical literature, particularly in specialist clinical journals. The aim of a cost of illness study is to identify and measure all the costs of a particular disease, including the direct, indirect, and intangible dimensions. The output, expressed in monetary terms, is an estimate of the total burden of a particular disease to society. It is widely believed that estimating the total societal cost of an illness is a useful aid to policy decision making, and indeed organszations such as the World Bank and the World Health Organization commonly use such studies (Byford *et al.*, 2000).

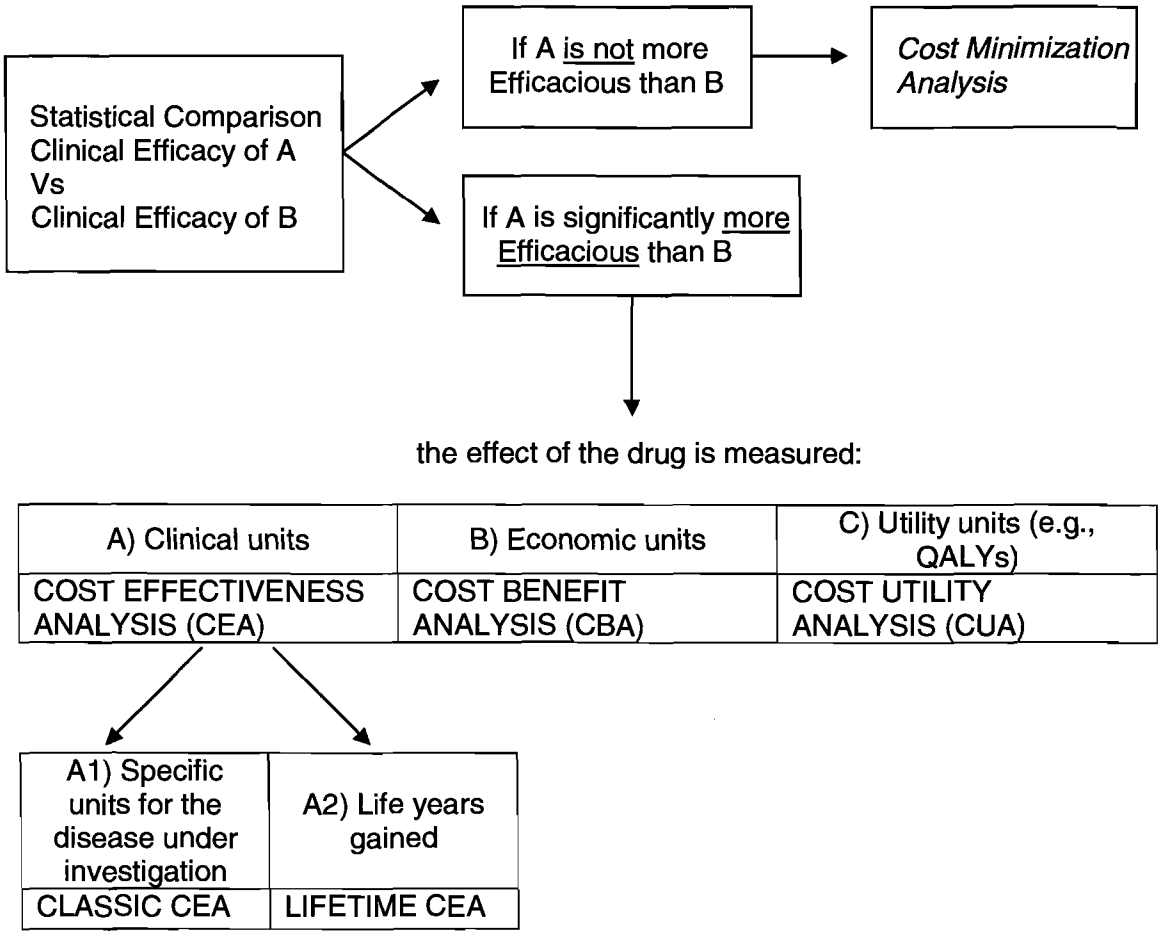
The cost of illness (COI) method itself has some obvious limitations. The methodology for estimating productivity losses, though well established, does not necessarily provide a reliable estimate in times of high unemployment. The true cost of lost productivity can only be assessed by detailed surveys of industry productivity and labour participation (Salkeld *et al.*, 1996).

3.5.5.6 Cost-consequences analysis (CCA)

CCA has been defined as an analysis in which costs and effects are calculated but not aggregated into quality-adjusted years or cost-effectiveness ratio. This type of analysis provides the most comprehensive presentation of information describing the value of a drug therapy or other health care interventions and is also conceptually the simplest (Salkeld *et al.*, 1996)(Orlewska *et al.*, 2001).

Figure 3.1 indicates the algorithm for the choice of pharmaco-economic interventions.

Figure 3.1: Algorithm for the choice of Pharmaco-economic interventions (Venturini *et al.*, 200: 11).



The algorithm can be used to identify the pharmaco-economic intervention for a statistical comparison between two products. Table 3.2 shows the pharmaco-economic interventions with the outcome measurements, descriptions as well as the advantages and disadvantages of each intervention.

Table 3.2 Types of pharmaco-economic studies (Venturini *et al.*, 2002: 10)

Method	Cost measure	Outcome Measure	Description	Advantages (A)/Disadvantages (D)
Cost-of-illness (COI)	R	Not applicable	Gives the total direct and indirect costs attributable to a given illness	Does not aid clinical choices (D) useful for the estimation of the economic burden of a disease (A)
Cost-minimization-analysis (CMA)	R	Any (usually clinical)	Find the lowest cost program among those shown to be of equal benefit	Rarely applicable (D) Only includes limited inputs (A)
Cost-effectiveness-analysis (CEA)	R	Clinical (physical units)	Years of life gives the cost per program-specific unit or year of live saved	Hard to make comparisons among studies or different diseases due to differences in the primary effectiveness measure (D) Broadly applied due to the wide range of possible clinical outcomes (A)
Cost-utility-analysis (CUA)	R	Outcomes that include patient preference (e.g., QALYs*, HYE's**)	Gives the cost per QALY or similar measure including the notion of patient preferences	It enables a broad range of outcomes to be combined in one summary outcome (A) Difficult to measure utilities (D)
Cost-benefit-analysis (CBA)	R	R	Full economic evaluation in which both inputs and outputs must be evaluated in monetary terms	It allows a direct comparison of the program incremental cost with consequences in commensurate units of measurement (A) Difficult to define a monetary for health consequences (D)

*QALY = Quality-adjusted life-year **HYE = Healthy-year equivalent

3.6 DIFFERENT TYPES OF COSTS AFFECTING PATIENTS

In a good pharmaco-economic evaluation, all relevant costs are included. Costs are broadly classified as direct, indirect and intangible costs. Direct costs include the cost of goods and services that can be purchased in the marketplace. Direct costs are further classified into medical and non-medical costs. Examples of direct medical costs are inpatient costs (e.g., laboratory tests, drugs, hospitalisation, etc.). In the case of pharmacological treatments, these include not only the cost of the drugs, but also the cost of their administration, clinical monitoring, costs for treatment of adverse events, etc. An example of a direct non-medical cost is transportation cost (Venturini *et al.*, 2002: 8).

According to Lacroix *et al.*(1995: 305) the cost of asthma can be divided into the following:

- Psychological cost.
  Patients with asthma display many differences, e.g. their disease may vary from moderate to severe. Patients may feel tired, tense, unsatisfied and depressed.
- Professional cost.
  Patients with acute exacerbations who need hospitalisations may feel guilty because of absenteeism from work and may show fear of losing their job.
- Cost of family life.
- Social cost

Severe asthma sufferers spend $12,813 a year per person in the USA caring for their asthma. A 5% shift from severe to moderate asthma would save approximately $1.4 billion annually in total costs, researchers (Cisternas *et al.*) concluded in a study in the June 2003, Journal of Allergy and Clinical Immunology.

According to the national asthma campaign of Queensland Health (2005) the costs of asthma would include the following:

- Pharmaceuticals.
- Medical consultations.
- Hospitals.

- Indirect medical.
- Allied health treatment costs.
- Total ambulance costs.
- Absenteeism.
- Lost productivity at work.
- Travel time for treatment.

Cost of illness studies provide insight into the economic impact of a disease. Some countries attempt to separate economic burden into disease-attributable direct and indirect costs. The direct cost is the value of health care resources devoted to diagnosis and medical management of the disease. Indirect costs reflect the monetary consequences of disability, missed work and school, premature mortality, and caregiver or family costs resulting from the illness. Data on these topics from developing countries are not available, but data from the United States and some European countries provide an understanding of the economic burden of COPD and asthma in developed countries (Chen *et al.*, 1999: 95).

A cross-sectional survey of 401 adults with asthma revealed that, while asthma medications make up the highest direct costs, indirect expenses might exceed the cost of drugs. Furthermore, per-person expenditures differ according to asthma severity (Cisternas, 2003: 1212)

3.6.1 DIRECT COSTS AFFECTING ASTHMA

Direct costs are those costs that can be identified specifically with a particular sponsored project, an instructional activity, or any other institutional activity, or that can be directly assigned to such activities relatively easily with a high degree of accuracy. Cost incurred for the same purpose in like circumstances must be treated consistently as both direct and indirect cost. Where an institution treats a particular type of cost as a direct cost of sponsored agreements, all cost incurred for the same purpose in like circumstances shall be treated as direct cost of all activities of the institution (Virginia Commonwealth University, 2002).

Direct costs of asthma include the following (Birnbaum *et al.,* 200: 95):

- Hospital care
  - Hospital inpatient care.
  - Emergency room visits.
  - Hospital outpatient care.
- Physician services
  - Physician outpatient care.
  - Physician office visits.
  - Prescription.

Work-related respiratory illness causes costs to the individual, employer and society as a whole. The most significant direct costs fall to individuals (and equivalently society) in loss of actual or potential income (equivalent to productivity), and in the suffering of those individuals involved. Direct costs are also incurred by firms in employee absence, administration and recruitment and retraining, although costs of absence are subsumed in the societal costs above. Finally, costs are incurred by society in medical treatment and recuperation (Health & safety executive, 2003).

Health and Safety Executive (2003) defines quantified costs as the loss of income through absence from work or through having to change jobs or take early retirement; expenditure on medical treatment; and pain and suffering of those affected.

In a study done by the American Academy of Allergy Asthma and Immunology on the direct costs of asthma, it was found that direct costs such as medication use and doctor visits, as well as the indirect costs of asthma, such as transportation times and loss of productivity at work. These factors were broken down for three levels of asthma: mild, moderate and severe. Researchers found a significant difference in direct and indirect costs between mild and severe asthma sufferers. Total costs for mild asthma sufferers averaged $2,646 per person, each year, while severe asthma sufferers averaged $12,813. The average spent for all asthma sufferers was $4,912 (AAAAI, 2003).

Direct costs arise from the health care services used in the prevention, diagnosis and treatment of the disease in question as well as rehabilitation services. It also includes private costs incurred by the patient and family and other public resources. If the incidence of hazardous substance-related disease were reduced, this would free

resources that would otherwise be used to diagnose and treat patients with HRID for some other purpose. It is important to note that such a reduction would not necessarily result in financial savings to the health care system. The value of fewer episodes of illness is the resources that are freed up for other uses (Salkeld *et al.*, 1996).

3.6.2 INDIRECT COSTS

Indirect costs are caused by lost output due to reduced productivity caused by absenteeism, temporary or permanent disability and premature mortality. This approach to valuing livelihoods is known as the human capital approach. The human capital approach values life as the value of forgone lost production (Salkeld *et al.*, 1996).

Fleurence (2003: 679) defines indirect cost as follows: indirect costs are associated with reduced productivity due to illness, disability and death. They are typically calculated from the gross earnings of those in employment. If the analysis is conducted from society's perspective, indirect cost should be included but, in practice, these costs are generally ignored.

They include not only the cost of absenteeism, reduced effectiveness whilst at work but also the cost of time taken attending medical appointments. No attempt has been made to place a financial value on the "quality of life" implications of asthma. Although the economic cost of lost productivity due to asthmatic illness can be valued in total terms, it cannot be assigned a monetary value at the individual level. An employed person may not suffer a direct reduction in income as a result of absenteeism or reduced productivity (National Asthma Campaign, 2005).

3.6.3 INTANGIBLE COSTS

The final group of costs and the most difficult to measure are the intangible or 'psychosocial' effects of illness. Pain, suffering or other reductions in quality of life are intangible and, by definition, difficult to quantify. Strictly, the intangible effects of illness are not costs, they are negative benefits. Economic costs are resources forgone in alternative use of those resources. As psychosocial effects do not have resource consequences *per se*, they should be placed on the benefit side of the

economic evaluation equation. As benefits are not included within the COI framework, they are not presented in this analysis (Salkeld *et al.*, 1996).

Fleurence (2003: 679) defines intangible cost as follows: Intangible costs relate to psychological costs associated with illness or treatment, such as pain and suffering. Although these costs may be mentioned in economic evaluations, they are rarely quantified because of the practical difficulties involved in doing so. Poor control of asthma, like severe asthma, can lead to a lower quality of life, greater need for medical care and hence increased cost to the community. Poor control is defined here as those adult asthmatics on sub optimal treatment regimens for a given level of disease severity (National Asthma Campaign, 2005).

3.7 THE COST-EFFECTIVENESS OF ASTHMA TREATMENT

Although asthma continues to be a high-cost disease, there are ways to manage the condition that can maximise outcomes and increase cost-effectiveness. These management ideas require an effective blend of proper medication choice and use, adequate non-pharmacological interventions, and education for patients, practitioners, and caregivers (Rational therapy, 2004).

3.7.1 INHALED CORTICOSTEROIDS

In a study done by Barnes *et al,.* (1999), inhaled corticosteroids form the mainstay of the treatment and management of asthma and the results of a meta-analysis comparing two of the most frequently prescribed inhaled corticosteroids, fluticasone propionate and budesonide, administered in a clinically equivalent 1:2 dose ratio to 1980 patients with asthma.

This study demonstrated that fluticasone propionate had an improved efficacy: safety ratio. Treatment with fluticasone propionate was more cost effective than budesonide with respect to improvement in morning peak expiratory flow rate, successfully treated weeks, symptom-free days, symptom-free 24 hours and episode free days. The main contributing factor to the higher cost of budesonide was the higher cost of health care contacts. The pharmaco-economic difference increased in favour of fluticasone propionate, as the criteria for success were made more stringent.

The results demonstrated that, for asthma patients requiring modification of therapy of treatment with fluticasone, propionate is more effective and also cheaper, in terms of overall health care costs, than treatment with budesonide.

In another study done by the Swedish Institute for Health Economics (Persson *et al.*, 2003: 1), they drew the attention to the study design, the weak correspondence between perspective and cost, and especially to the impact of bias in health economic results when comparing different doses of inhaled corticosteroids (ICSs). Persson tried to determine whether published cost-effectiveness studies on ICS in asthma adhered to basic analytical standards as defined in health economics textbooks and in guidelines assessing and comparing efficacy and safety (Persson *et al.*, 2003: 1).

3.7.2 B_2-AGONISTS

The literature directly comparing leval-buterol and racemic albuterol in terms of cost effectiveness is limited but compelling. Cost effectiveness can also be inferred from clinical data showing a reduced need for hospitalisation. Although medication accounts for the greatest portion of direct medical costs for asthma management on a population basis, those patients who require hospitalisation incur greatly increased costs (Quinn, 2004: s154).

In a study done by Lindgren *et* al. (2005: 62), the aim was to evaluate the cost-effectiveness of formoterol (Oxis®) Turbuhaler® 4.5 µg and salbutamol 200 µg as reliever medications in Sweden and Spain. Total health care costs were not significantly different between formoterol and salbutamol dry powder inhalers in Sweden, whereas in Spain, the health care costs were 20% higher for formoterol vs. salbutamol pressurised metered dose inhalers. Total health care costs increased with disease severity, defined according to the Global Initiative for Asthma guidelines. Compared with salbutamol, formoterol produced statistically significant improvements in effectiveness, less reliever and maintenance medication usage, reduced health care resource utilisation, with no increase or a limited increase in health care cost (Lindgren *et* al., 2005: 62).

3.7.3 COMBINATIONS

In a study done by Anderson *et al.* (2001: 505) adding formoterol to corticosteroid established therapy has a clear clinical benefit. The primary objective of their study was to asses the health economics of adding long-acting β_2-agonist formoterol to the inhaled corticosteroid budesonide in the treatment of asthma. Savings from reduced use of resources for exacerbation offset the extra costs of adding the inhaled ß2-agonist formoterol to the corticosteroid budesonide in asthmatic patients in Sweden.. Anderson *et al.* concluded that adding the inhaled long-acting ß2 agonist formoterol to low moderate doses of the inhaled corticosteroid budesonide generated significant gains in all outcome measures with partial or complete offset of costs. Adding formoterol to budesonide can thus be considered to be cost effective (Anderson *et al.*, 2001: 505).

Asthma guidelines recommend an inhaled corticosteroid plus a long acting inhaled β_2-agonist (β_2-adrenoceptor agonist) as preferred maintenance therapy for moderate and severe persistent asthma. The clinical effectiveness of salmeterol/fluticasone propionate in patients with persistent asthma symptoms has been established in comparative clinical trials (Lyseng-Williamson *et al.*, 2003: 952).

Pharmaco-economic analyses, based on data from these clinical trials, have been conducted from a health care payer perspective in various countries. In patients with asthma not controlled with inhaled corticosteroids, salmeterol/fluticasone propionate was associated with more favourable cost-effectiveness ratios than fluticasone propionate monotherapy, oral montelukast plus inhaled fluticasone propionate, inhaled budesonide, and inhaled formoterol plus budesonide (Lyseng-Williamson *et al.*, 2003: 952).

3.8 MEDICAL SCHEMES ACT AND REGULATIONS

The Medical Schemes Act of South Africa (no. 131 of 1998) states:

To consolidate the laws relating to registered medical schemes; to provide for the establishment of the council for the medical schemes as a juristic person; to provide for the appointment of the Registrar of Medical schemes; to make provision for the registration and control of certain activities of medical schemes; to protect the

interests of members of medical schemes; to provide for measures for the co-ordination of medical schemes; and to provide for incidental matters.

The medical schemes act was amended and new regulations gazetted during the period under review, so as to ensure that schemes would be forced to observe the ideals in the medical schemes act. Regulations gazetted in Novernber 2002 seek to compel trustees to disclose what they earn as trustees to members of the medical scheme to strengthen governance requirements. They also broadened the prescribed minimum benefits and included minimum conditions under which treatment could take place to ensure that the chronically ill were not discriminated against (Council for Medical schemes, 2003: 11).

Prescribed minimum benefits package under section 29 (1) (o) of the Medical schemes act:

"Minimum accumulated funds to be maintained by a medical scheme."

In this regulation "accumulated funds" means the nett asset value of the medical scheme, excluding funds set aside for specific purposes and realised non-distributable reserves.

3.8.1 PRESCRIBED MINIMUM BENEFITS

With the introduction of Prescribed Minimum Benefits (PMB) for the diagnosis, medical management and medication of a number of chronic disease states, many schemes are introducing changes to their medical benefits in 2004 (Medscheme, 2004). PMB were introduced to avoid incidents where individuals lose their medical scheme cover in the event of serious illness and are put at serious financial risk due to unfunded utilisation of medical services. They also aim to encourage improved efficiency in the allocation of private and public health care resources (Council for Medical Schemes, 2005). New regulations also continued the development of the package of prescribed minimum benefits (PMB). These included the extension of the package to 25 chronic conditions that schemes will have to cover and that came into effect in January 2004 (Council for Medical Schemes, 2002: 12).

The PMB include the 27 chronic disease conditions, listed as the Chronic Disease List (CDL). The Minister of Health has published amendments to the general regulations of the Medical Schemes Act; No 131 of 1998 in the Government Gazette No. 25537 dated 6 October 2003 under Notice No. 1397. This publication includes the treatment algorithms and the relevant ICD-10 diagnostic codes for the Chronic Disease List (CDL) (Mediscor, 2005). Various factors were taken into account when identifying the diseases that would be covered, such as; the nature of the disease and how that disease would affect the quality of life of the individual; the most prevalent conditions; the affordability of the treatment and the financial impact on medical schemes (Council for Medical Schemes, 2005).

The following chronic conditions (listed alphabetically) are covered under the PMB benefit. If the patient suffers from one or more of the listed conditions, medicine treatment and care of these will be covered with no limits, subject to your scheme's applicable rules and registration procedures (Mediscor, 2005):

The Chronic Disease List is a list of 27 chronic conditions, which have to be covered by all medical schemes from January 2004. Asthma is one of them.

The 27 chronic conditions are:

- Addison's disease;
- Asthma;
- Bipolar mood disorder (or manic depression);
- Bronchiectasis;
- Cardiac failure;
- Cardiomyopathy;
- Chronic obstructive pulmonary disorder;
- Chronic renal disease;
- Coronary artery disease;
- Crohn's disease;
- Diabetes insipidus;
- Diabetes mellitus types 1 & 2;
- Dysrhythmias;
- Epilepsy;
- Glaucoma;
- Haemophilia;

- Hyperlipidaemia;
- Hypertension (or high blood pressure);
- Hypothyroidism;
- Multiple sclerosis;
- Parkinson's disease;
- Rheumatoid arthritis;
- Schizophrenia;
- Systemic lupus erythematosus; and
- Ulcerative colitis.

3.9 NEW MEDICINE PRICING REGULATIONS

From 27 August 2004, pharmacists were no longer able to put a mark-up on medicines in the way this happened before. Instead, they were only allowed to charge the following dispensing fees (exclusive of VAT) (TAC electronic newsletter, 2005):

Pharmacists:

For each schedule 1 and 2 medicine without a prescription – 16% of the single exit price (SEP) up to a maximum of R16.

For each schedule 3,4,5,6,7 and 8 medicine (and schedule 1 and 2 medicine with a prescription) – 26% of the SEP up to a maximum of R26

Dispensing doctors:

For all medicines regardless of scheduling, 16% of the SEP with a maximum of R16

3.9.1 ESTABLISHMENT OF THE SINGLE EXIT PRICE (SEP)

The pricing regulations set out two mechanisms in terms of which the manufacturer or importer of a medicine would determine a particular medicine's single exit price:

The first mechanism, which came into effect on 2 June 2004, removed the "cost" of incentive schemes such as bonuses, rebates and discounts. This effectively averaged prices out (at 2003 levels) without making any significant difference to the manufacturers' bottom lines (TAC electronic newsletter, 2005).

The second mechanism was somewhat more complex. It involved the development – by the Director-General of Health (DG) – of a "methodology for conforming with international benchmarks". This was to ensure that medicine prices in South Africa would be in line with those in other countries where medicine prices are regulated. Manufacturers and importers were to have three months to adjust their SEPs once the DG had published the "methodology". This process may very well have resulted in a significant reduction in medicine prices, particularly if comparisons were made with developing countries like India. But until the DG acted – and the regulations did not say when this would be – the first mechanism would continue to be used (TAC electronic newsletter, 2005).

3.10 GENERIC SUBSTITUTION

A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, and route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies in America. Even more billions are saved when hospitals use generics (FDA/Centre for Drug Evaluation and Research, 2005).

Generic drug products that have been approved by the FDA (Food and Drug Administration) must meet the same rigorous standards for safety and effectiveness as brand-name drugs. In addition to being safe and effective, the generic product must have the same active ingredient or ingredients, be the same strength, and have

the same labelling for the approved uses as the reference brand product. The generic product must also be available in the same dosage form, and have the same route of administration as the brand name product. Thus, generic products will perform the same as their respective reference brand products. Similarly, generic manufacturing and packaging sites must pass all of the same quality standards as those of brand name drugs and the generic products must meet the same specifications as any approved new drug product (Buehler, 2004).

Many products that do not use chlorofluorocarbons (CFC) are already available for the treatment of asthma and chronic obstructive pulmonary disease. These products are not necessarily "official" direct alternatives to CFC Metered Dose Inhalers but may in many patients serve as a useful medication that could replace the need for a particular CFC Metered Dose Inhaler. The FDA will determine official alternatives by using the criteria established through notice-and-comment rulemaking, as it has done with albuterol.

Generics have long offered a safe and inexpensive alternative to many brand-name drugs. Using average national retail price data from IMS Health's National Prescription Audit *Plus*^{TM}, the drug costs have been calculated per-day for several different hypothetical patients. This show that the drug costs per day can fall by 14 to16 per cent if patients use generics instead of branded drugs, depending on their medical needs. Patients whose needs can be fully satisfied with generics could enjoy reductions of 52% in the daily costs of their medications (FDA/Centre for Drug evaluation and Research, 2004).

The FDA examined six hypothetical patients, and calculated two costs for each patient. The first cost estimate was for the case where all drugs were branded products. The second cost estimate was for the case where the patient bought generic versions if they were available. The six hypothetical patients included one who was prescribed only off-patent products, two who were prescribed only on-patent products, and three that were prescribed a mix of both (FDA/Centre for Drug Evaluation and Research, 2004).

3.11 CHAPTER SUMMARY

Asthma takes a tremendous toll on those people who suffer from the disease, as well as on the health care system. Some recent studies have shown that including levalbuterol as part of asthma therapy can reduce costs in terms of ED visits and hospital stays. Such findings indicate the value of examining the cost-effectiveness and outcomes of asthma treatment in both inpatient and outpatient settings. This can be done via cost-benefit analyses and other outcomes studies that document, track, and monitor set values in a consistent fashion over time.

Pharmaco-economic principles and methodology are useful tools for making decisions in health care, given the limited resources available. Although the discipline is still in development, recent advancements have resulted in the recognition that pharmaco-economics is required when evaluating new health care interventions. Pharmacists are in a position to routinely apply these tools in day-to-day practice, quantifying the value of pharmaceuticals in balancing costs and outcomes. The addition of this knowledge to the clinical background of the pharmacist provides qualifications that enhance the profession in the best interest of patients, health care systems and society.

In the next chapter the research methodology will be discussed.

CHAPTER 4
RESEARCH METHODOLOGY

4.1 INTRODUCTION

In this chapter the research methodology followed in this study will be discussed. The procedures followed in acquiring the information and the subsequent analysis of the data will be discussed. The objectives of the empirical investigation, data source, database, and empirical research method will be discussed.

4.2 OBJECTIVES OF THE EMPIRICAL INVESTIGATION

The general objective of this study was to review the medicine management of asthma in the private health care sector in South Africa through a managed pharmaceutical care approach.

The specific research objectives were as follows:

- To investigate the prevalence of asthma in the general public.
- To conceptualise what asthma together with its management entails.
- To determine which pharmaceutical care principles should be followed in the management of asthma.
- To determine the spectrum of anti-asthma agents and how they have changed through the years.
- To conceptualise what pharmaco-economic implications entail.
- To conceptualise what pharmaco-epidemiology entails.
- To determine through the literature study what the medical treatment of asthma costs.
- To determine what the relevance and frequency of generic substitution of the different categories of anti-asthma agents are.
- To determine the prevalence and cost of the different anti-asthmatic agents.
- To investigate the influence of the "new" medicine pricing system as implemented during 2004 on the cost of anti-asthmatic agents.
- To compare the prevalence of asthma medication of 1995 with the prevalence of asthma medication of 2004.
- To investigate the rationality of combination asthma therapy.

4.3 RESEARCH METHODOLOGY

4.3.1 THE DATA SOURCE

The data for this study were extracted from the database *Interpharm* Datasystems® in South Africa for a 12-month period, from the 1st January 2004 to 31st December 2004. Data were analysed with the aid of the *Statistical Analysis System* SAS 8.2® computer package.

4.3.2 COMPOSITION OF THE ASTHMA STUDY POPULATION

The asthma study population was composed in the following manner:

- All of the patients that had used one or more of the asthma-related medications between 1 January 2004 and 31 December 2004 were taken into account.
- All of the cases that indicated a cost component were included.

The asthma study population was extracted from the total population and represents 115 684 (4.46%) of the 2 595 254 prescriptions on the database.

4.3.3 SELECTION OF CRITERIA AND MEASURING INSTRUMENTS FOR DATA ANALYSIS

The following were used as criteria/measuring instruments for the analysis of the data:

4.3.3.1 PREVALENCE

Prevalence is a statistic of primary interest in public health because it identifies the level of burden of disease or health-related events on the population and health care system (U.S. National Institute of Health, 2004). Prevalence represents new and pre-existing cases alive on a certain date, in contrast to incidence, which reflects new cases of a condition diagnosed during a given period of time. Prevalence is a function of both the incidence of the disease and survival (U.S.

National Institute of Health, 2004). For the purpose of this study, prevalence and number of asthma patients, are viewed as synonyms. Prevalence (N = 115 684) and incidence are also used interchangeably. The prevalence figure is then dependent on asthma medicine usage.

4.3.3.2 COST

The prescribed treatment may be defined as the medication provided to the patient, and was determined from the database. In this study the total cost, average medicine treatment cost and the minimum and maximum treatment costs will be investigated. The influence of the "new" medicine pricing regulations (single exit price 2004) on the cost of asthma-related medication will also be investigated.

4.3.3.3 STATISTICAL ANALYSIS

The following statistical methods were used to investigate the data according to the measuring instrument criteria as discussed in section 3.3.

Average value (mean)

A description of a distribution almost always includes measures of its centre or average. The most common measure is the ordinary *arithmetic average*, or mean (Moore, 1995: 36).

The arithmetic mean of a set of n measurements y_1, y_2, y_3 ...yn is equal to the sum of the measurements divided by n (Mendenhall, 1982: 48).

$$\text{Mean} = \bar{y} = \frac{\Sigma y}{N}$$

Where y = the values of the variable,

Σ = the sum of

n = number of observations.

Standard deviation

The **variance s^2** of a set of observations is the average of the squares of the deviations of the observations from their mean. In symbols, the variance of *n* observations is $x_1, x_2, \ldots, x_n$ (Moore, 1995: 46):

$$S^2 = \frac{(x_1 - \bar{x})^2 + (x_2 - \bar{x})^2 \ldots\ldots + (x_n - \bar{x})^2}{n - 1}$$

The standard deviation s is the square root of the variance s^2:

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

Where:s = standard deviation

n = the number of observations

Range

One way to measure the spread is to calculate the range, which is the difference between the largest and smallest observations (Moore, 1995: 41).

$$Range = x_{max} - x_{min}$$

Effect sizes

The d-value used was to calculate the practical significance of the differences between prescribed average medicine costs. The d-value can be calculated by the following formula (Steyn 1998:3):

$$d = \frac{Ya - Yb}{S\max}$$

Where: Ya = the average medicine treatment cost of medicine a

Yb = the average medicine treatment cost of medicine b

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

Steyn (1998:3) recommends the following as guidelines:

[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

Cost prevalence index

The cost index can be calculated by means of the following formula (Serfontein, 1989: 180):

$$\text{Cost index} = \frac{\%\ Cost\ of\ treatment}{\%\ Prevalence\ of\ asthma\ medicine\ items}$$

The results can be interpreted with the following aid:

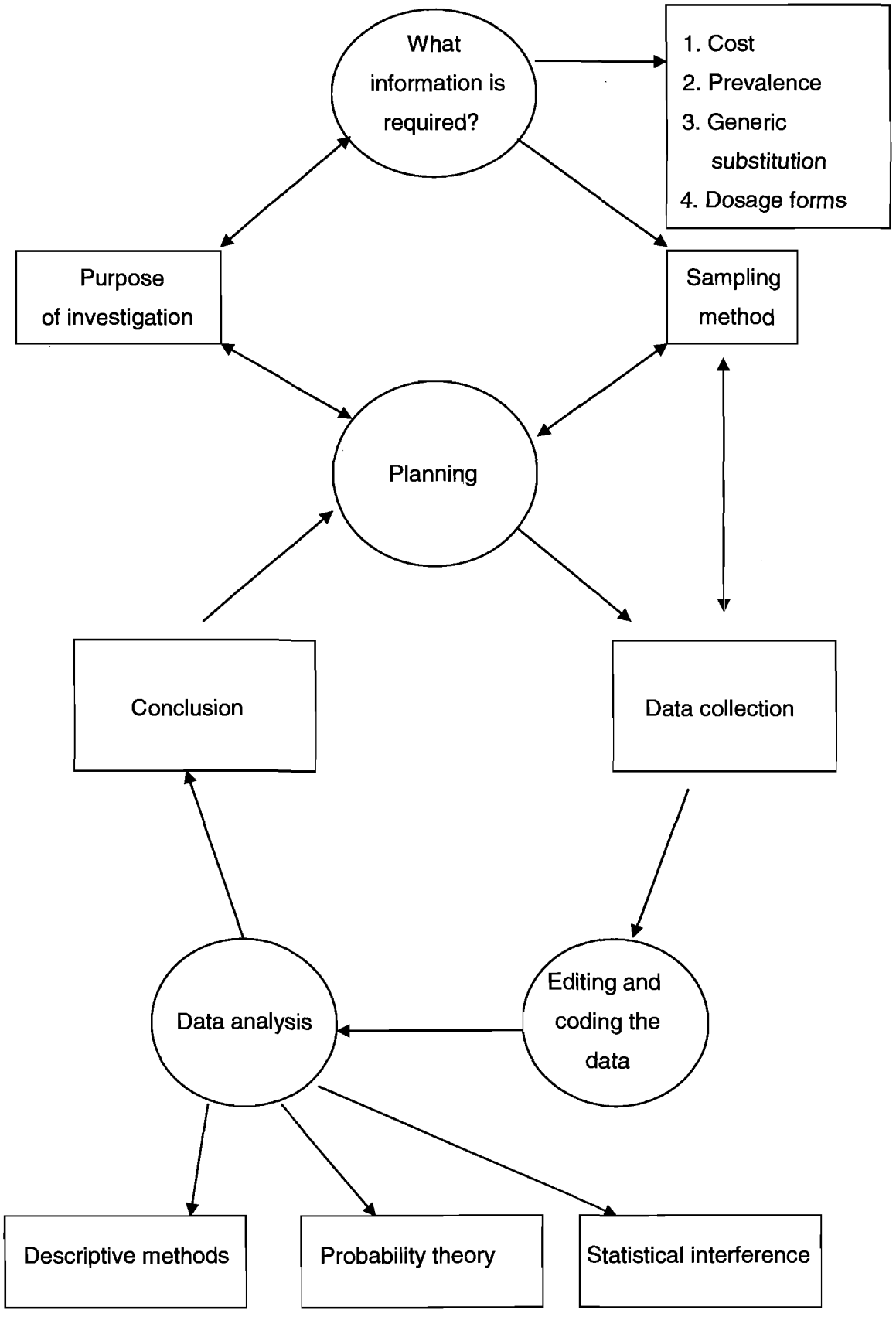
If cost index < 1: therapy utilised is relatively inexpensive.
If cost index = 1: equilibrium exists between the cost and the prevalence of therapy.
If cost index > 1: therapy utilised is relatively expensive.

Weighted average

The average is used when calculating a collective average of various data sets. Where n_i and x_i represent the size and average of the i-set, i=1, 2, 3,.....k (Steyn *et al.*, 1994: 102).

For the purpose of this study the weighted average was calculated by means of the statistical function of a scientific calculator.

Figure 4.1 The role of statistics in research projects and other investigations (Steyn, 2003: 4)



The purpose of the study and the planning of what information to use were done first (see 4.2 Objectives of the empirical investigation). For this study the data were provided by *Interpharm Datasystems®* in South Africa. Data analysis, descriptive methods and the conclusion was the main part of this study.

4.4 RELIABILITY AND VALIDITY

The data were obtained from the *Interpharm Datasystems®* in South Africa and no direct manipulation of the data by the researcher was possible. The research was conducted under the impression that all data obtained from the database were precise and correct. The data obtained and analysed from the data source can be generalied to the database and the specific study population only.

4.5 CHAPTER SUMMARY

The empirical research method was discussed in this chapter. The general and specific research objectives of the empirical investigation, data source and empirical investigation methodology were discussed.

The results of the empirical investigation will be reported in Chapter 5.

CHAPTER 5
RESULTS AND DISCUSSIONS

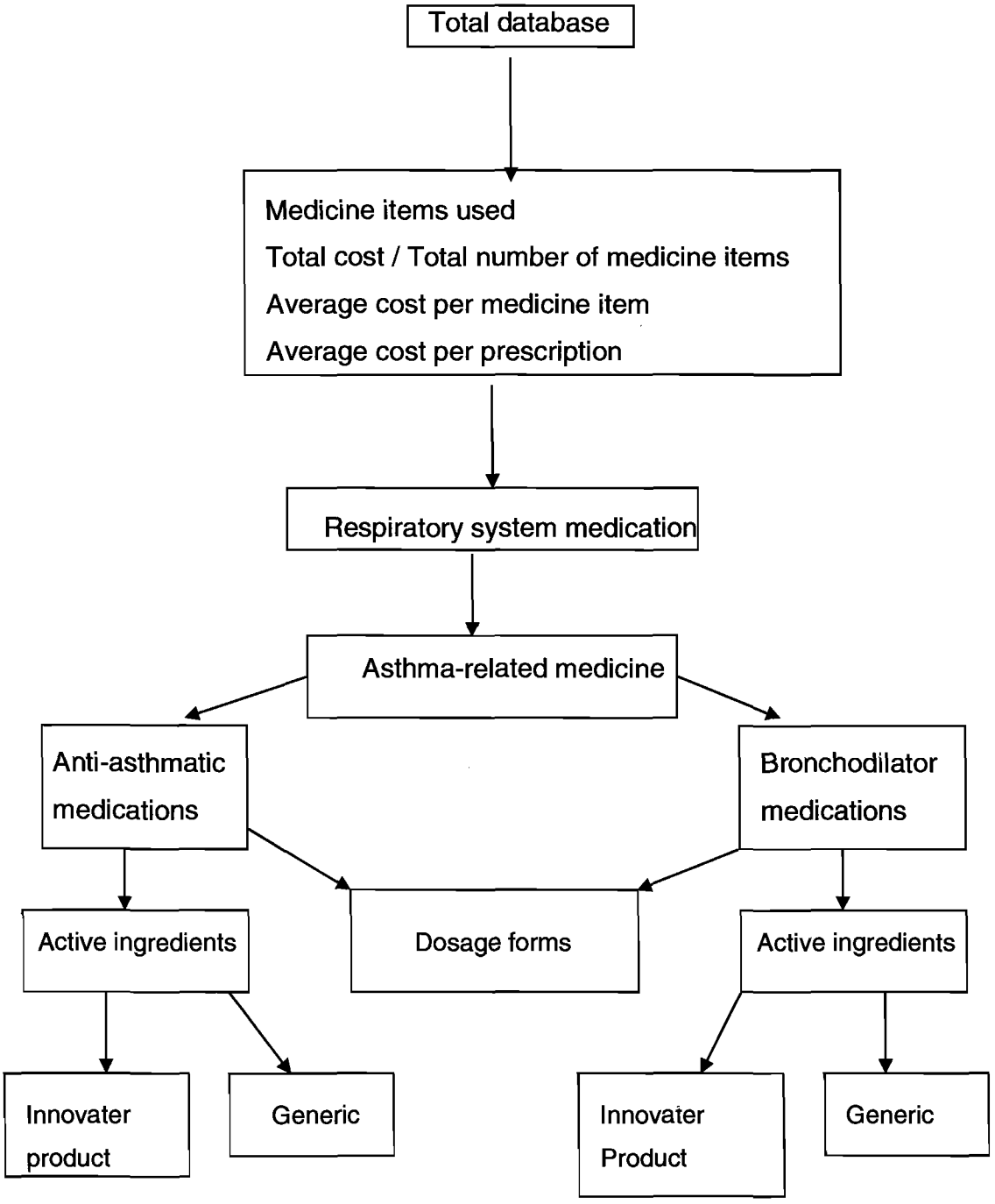
5.1 INTRODUCTION

In this chapter the results of the empirical investigation of the usage and cost of anti-asthmatic medicine for the study period from 1st January to 31st December 2004 will be discussed. The study period was divided into three periods, January to April, May to August and September to December.

From January to April there were no limitations on the pricing structure of medicine (before the introduction of the single exit price, also referred to as the pre-single exit price period). The new legislation (single exit price system, SEP) came into effect during May 2004 and changed the pricing structure of medication in South Africa. May to August 2004 is referred to as the interim period, where the new regulation was to be phased in. As from September 2004 the new pricing regulation was "fully" implemented, therefore September to December can be referred to as the post-single exit price period.

Figure 5.1 explains the presentation of the results for the study period.

Figure 5.1 Organogram representing the presentation of the results



5.2 DEFINITIONS

The following terms were used in this chapter and their meaning or definition for the purpose of this study will be as follows:

Prescription: A prescription is a list of medication prescribed by a recognised practitioner for a patient. This list contains *medicine items* and *asthma medicine* or other treatments, which will be used in the treatment of a disease or sickness. For the purpose of this study only prescriptions listed on the database during the study period will be taken into consideration.

Asthma-related medicine: Asthma-related medicine refer to medicine that is directly related to the treatment of asthma. For this study asthma medication will include only the bronchodilators and the anti-asthmatic groups in the treatment of the disease (Listed in MiMS® April, 2004 under the headings of 10.2 and 10.4). In this context asthma-related medicine must not be confused with medicine that may introduce asthma attacks, but medication used for the treatment of asthma as a disease as defined in this study.

Anti-asthmatic medication: As part of asthma-related medicine it refers to medicine directly related to the treatment of asthma. (see asthma-related medicine above).

Medicine items: Medicine items are items that contain an active therapeutic agent prescribed on a legal prescription used in the treatment and management of all disease conditions, including asthma.

Total database: The total database includes all medication items prescribed and claimed during the different study periods. This includes all *medicine items* on all the prescriptions, but excludes non-medicine

items e.g. bandages, catheters and other non-active containing ingredients or products.

Study population: The study population consists of all the prescriptions claimed for patients of different medical aids and managed by *Interpharm Data Systems®* for the specific study period.

Patient: This will be the person to whom the prescription was issued and who claimed accordingly and who will be treated during the study period for all conditions including asthma. For the purpose of this study a person and a prescription may be viewed as synonyms.

Respiratory system medication: This includes all medication used for the treatment of any respiratory disease in the following groups (as based in the MiMS® under the headings of 10.2 and 10.4):

- Coughs and colds
- Bronchodilators
- Mucolytics
- Anti-asthmatics
- Surfactants

Innovator product: A brand product that is referred to as the original/innovater research, and patented as the original product.

Generic product: A product that contains the same active ingredient as the original innovator product, but is not patented as the original/innovator product.

5.3 THE PREVALENCE AND COST OF MEDICINE ITEMS AND PRESCRIPTIONS ON THE DATABASE IN GENERAL

Table 5.1 below illustrates the prevalence of asthma vs. the total database in terms of quantities and costs.

Table 5.1 The prevalence and cost of medicine items and prescriptions on the database for 2004 (1 January 2004 to 31 December 2004)

	Total data base	Asthma-related medication
Total number of prescriptions	2 595 254	115 684
Total number of medicine items	5 305 882	154 851
Average number of medicine items per prescription*	2.04 (±0.09)	1.34 (±0.60) (N = 115 684)
Maximum number of medicine items per prescription	18	6
Total cost of medicine items (R)	R 661 223 146.00	R 29 567 363.00
Weighted average cost per medicine item (R)*	R 124.62 (±R36.96) (N =3)	R 190.94 (±R219.25) (N =154 851)
Average cost per prescription*	R 254.78 (±R53.88) (N =3)	R 255.59 (±283.35) (N =115 684)

*A weighted average was calculated from the averages of the three study periods to obtain an average for the total study period

It was found that 4.46% of all prescriptions (total database) contained at least one asthma-related medication. Of the 5 305 882 medicine items that were claimed during 2004, 2.92% (N = 154 851) were asthma-related medication. The total cost of asthma-related medication amounted to R 29 567 363.00, thus representing 59.08%
(R 50 050 013.28) of the respiratory system medication on the database and 4.47% of the cost of the total database medication (N = R 661 223 146.00). (Refer to table 5.1)

Table 5.2 The prevalence and cost of medicine items and prescriptions on the database for the three study periods.

	January to April 2004		May to August 2004		September to December 2004	
	Total data base	Asthma-related medication	Total data base	Asthma-related medication	Total data base	Asthma-related medication
Total number of prescriptions	713 475	30 474	935 644	42 400	946 135	42 810
Total number of medicine items	1 363 585	40 339	1 953 845	55 820	1 988 452	58 692
Average number of medicine items per prescription	1.91 ±1.21	1.32 ±0.59	2.09 ±1.29	1.32 ±0.61	2.10 ±1.30	1.37 ±0.62
Maximum number of medicine items per prescription	18	6	18	8	17	6
Maximum price of a prescription	R 147 426.25	R 22 088.21	R51 207.71	R 50 976.76	R70 628.02.	R 6 011.02
Maximum price of item	R 92 097.44	R 21 792.28	R50 785.50	R 50 785.50	R58 446.72	R 6 011.02
Total cost of medicine items (R)	R198 934 122	R9 223 429.87	R242 721 616	R10 639 178.13	R219 567 408	R9 704 755.00
Average cost per medicine item (R)	R145.89 ±R283.72	R228.65 ±R227.50	R124.23 ±R208.03	R190.60 ±R272.31	R110.42 ±R202.84	R165.35 ±R138.35
Average cost per prescription (R)	R278.82 ±R476.38	R302.67 ±R300.79	R259.42 ±R370.98	R250.92 ±R338.10	R232.07 ±R354.89	R226.69 ±R192.14

From table 5.2 it could be gathered that the prevalence of prescriptions containing asthma medication remained relatively consistent at 4.27% (N = 30 474) for the first period, 4.53% (N = 42 400) for the second and 4.52% (N = 42 810) for the last. This was the same for the total number of asthma medicine items per prescription, with only a slight increase during the last period.The total cost of asthma medication for each period represented; 4.63% (N = R9 223 429.87), 4.38% (N = R 10 639 178.13) and 4.42% (N= R 9 704 755.00) of the cost of medicine for each period on the total database. The average cost per medicine item and average cost per prescription of asthma medicine was higher during each period than that of the average total database. The effect of the new medicine pricing regulations on the ***average cost per medicine item*** was more visible on asthma medicine with a price difference of R63.30 from the first period to the last. The decrease in the average cost per medicine item on the total database as a result of the new medicine pricing regulations was R 35.47. (Refer to table 5.2)

During the period 1 January to 30 April 2004, a total of 713 475 prescriptions were claimed representing 1 363 585 medicine items. The average number of medicine items per prescription was 1.91 ±1.21, with a minimum of 1 and a maximum of 18 medicine items per prescription. The total cost for all medicine items was R198 934 122.00. (Refer to table 5.2)From the database the average cost per prescription for the total database for the period 1 January 2004 to 30 April 2004 was calculated at R278.82 ±R476.38 *per prescription.* For this period the minimum cost of an item on a prescription was R0.01 with a maximum cost of R 147 426.25. The average cost per item was R145.89 *per item.* The minimum price for an item on a prescription was R0.01 with a maximum price of R92 097.44. (Refer to table 5.2)

During the period May to August 2004, 935 644 prescriptions were claimed which contained a total of 1 953 845 medicine items. There were on average 2.08 ± 1.29 medicine items per prescription. The minimum number of medicine items on a prescription was one and the maximum number of medicine items on a prescription was 18. The total cost of these medicine items was R242 721 616.00. The minimum cost per prescription was R0.01 with a maximum cost of R51 207.71. The average cost *per prescription* for the total database for this period was R259.42 ±R370.98. On average the patient paid R124.23 ±R208.3 per *medicine item* during this period with no item less than R0.01 or more than R50 785.50. (Refer to table 5.2)

Table 5.3 The prevalence (items) of the top 10 pharmacological groups for the period January to April 2004.

	Main pharmacological group	Prevalence medicine items (N= 1 363 585)	Percentage prevalence (%)
1.	Cardio-vascular agents	203 413	14.92
2.	Antimicrobials	149 033	10.93
3.	***Respiratory system***	*142 835*	*10.47*
4.	Endocrine system agents	128 845	9.45
5.	Central nervous system agents	128 169	9.40
6.	Analgesics	112 820	8.27
7.	Musculo-skeletal agents	82 500	6.05
8.	Gastrointestinal tract agents	79 135	5.80
9.	Ear, nose and throat agents	57 546	4.22
10.	Dermatological agents	51 826	3.80

Table 5.4 The prevalence (items) of the top 10 pharmacological groups for the period May to August 2004.

	Main pharmacological groups	Frequency (N=935 644)	Percentage prevalence (%)
1.	**Respiratory system**	*286 615*	*14.67*
2.	Antimicrobials	268 850	13.76
3.	Cardio-vascular agents	239 798	12.27
4.	Analgesics	178 653	9.14
5.	CNS	156 546	8.01
6.	Endocrine system	149 812	7.67
7.	Musculo-skeletal agents	111 411	5.70
8.	Gastro-intestinal tract	100 825	5.16
9.	Ear, nose and throat	92 981	4.76
10.	Dermatological	67 689	3.46

Table 5.5 The prevalence (items) of the top 10 pharmacological groups for the period September to December 2004.

	Main pharmacological group	Frequency	Percentage prevalence (%)
1.	Cardio-vascular agents	282 567	14.21
2.	Anti-Microbials	264 574	13.31
3.	***Respiratory system***	***199 304***	***10.02***
4.	Analgesics	173 459	8.72
5.	CNS	172 285	8.66
6.	Endocrine System	166 896	8.39
7.	Gastro-intestinal tract	114 863	5.78
8.	Musculo-skeletal agents	114 161	5.74
9.	Ear, nose and throat	85 373	4.29
10.	Dermatologicals	80 461	4.05

For the period between September and December 1 988 452 medicine items were prescribed on 946 135 prescriptions. An average of 2.10 ±1.30 items was prescribed per prescription. The minimum number of items on a prescription was 1 with a maximum of 17 items. The total cost of these items during this study period was R219 567 408. (Refer to table 5.2)On average, each *item* cost the patient R110.42 ±.R202.84. No drug cost less than R0.01 and none more than R58 446.72. This also gave a mean value of R232.07 ±R354.89 *per prescription* with a minimum value of R0.01 and a maximum cost of R70 628.02. (Refer to table 5.2)

The total number of respiratory system items (N = 628 754) represented 11.85% of all medicine items claimed and contributed 7.57% (R 50 050 013.28) of the total cost of all medicine items claimed during this study period. (refer to tables 5.3, 5.4 and 5.5)
Asthma-related medication for this study consists of two pharmacological subgroups (as based in the MiMS® under the headings of 10.2 and 10.4):

- Bronchodilators
- Anti-asthmatics

The bronchodilators consist of the following pharmacological products:

- Sympathomimetics
- Methylxanthines and combinations
- Anticholinergics.

The anti-asthmatics for this study include the following pharmacological products (as based in the MiMS® April 2004):

- Glucocorticoids
- Leukotiene receptor antagonists
- Chromones
- Other anti-asthmatics

Figure 5.2 Percentage prevalence of the asthma-related medicine items for the three study periods 2004.

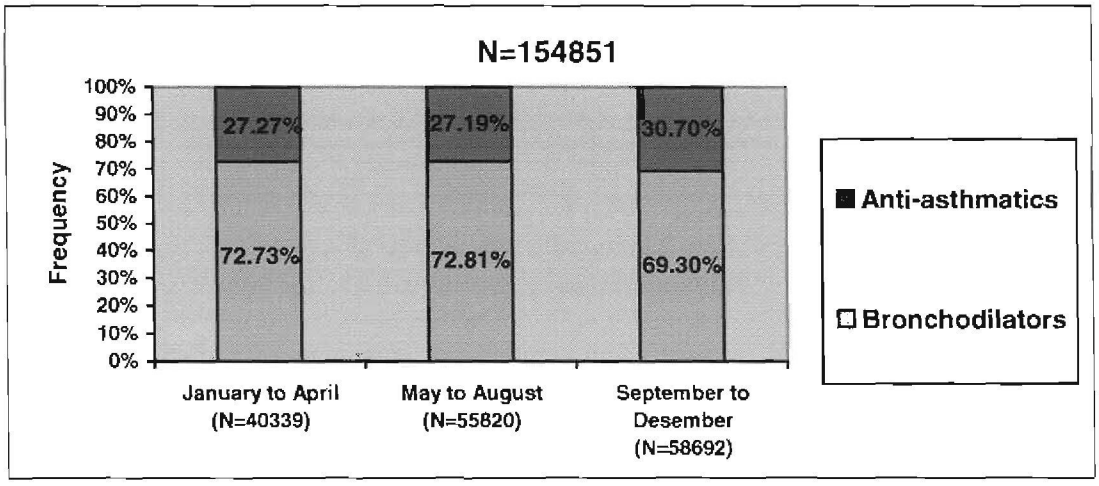


Figure 5.2 indicates the percentage prevalence of the anti-asthmatics and the bronchodilators (as based in the MiMS® under the headings of 10.2 and 10.4) for each of three study periods during 2004. The prevalence of bronchodilators for each of the three periods was much higher than that of the anti-asthmatics

Table 5.6 The total number of bronchodilator medicine items claimed during the study period 1 January to the 31 December 2004

Study period	Frequency of bronchodilator items	Total database (%)	Respiratory system agents (%)	Asthma-related medicine items (%)
January to April	29337	2.15 (N =1 363 585)	20.54 (N =142 835)	72.73 (N = 40 339)
May to August	40641	2.08 (N =1 953 845)	14.18 (N=286 615)	72.81 (N = 55 820)
September to December	40672	2.05 (N =1 988 452)	20.40 (N =199 304)	69.30 (N = 58 692)
Total:	**110650**	**2.09 (N= 5 305 882)**	**17.60 (N = 628 754)**	**71.46 (N = 154 851)**

In table 5.6 it can be seen that 110650 bronchodilator items were claimed during 2004. This represented 2.09% of the total number of medicine items claimed (N = 5305882) and 17.60% of the total number of respiratory system agents claimed (N = 628754 items). The asthma-related medication claimed during 2004 represented 2.92% of the total database thus the bronchodilators contributed 71.46% of the asthma medication used (N= 154 851). (Refer to tables 5.1 and 5.6)

Table 5.7 The total number of anti-asthmatic medicine items claimed during the study period 1 January to the 31 December 2004.

Study period	Frequency of anti-asthmatic items	Total database (%)	Respiratory system agents (%)	Asthma-related medicine items (%)
January to April	11 002	0.81 (N=1 363 585)	7.70 (N =142 835)	27.27 (N=40 339)
May to August	15 179	0.78 (N=1 95 3845)	5.30 (N=286 615)	27.19 (N=55 820)
September to December	18 020	0.91 (N=1988452)	9.04 (N=199 304)	30.70 (N=58 692)
Total:	**44 201**	**0.83 (N= 5 305 882)**	**7.03 (N= 628 754)**	**28.54 (N = 154 851)**

In the period 1 January to the 31 December 2004 the total number of anti-asthmatic items claimed was 44201. This represented 0.83% of all the medicine items on the database (N = 5 305 882), and contributed 28.54% of the total number of asthma-related medicine items claimed (N = 154 851). The anti-asthmatics contributed 7.03% of all the respiratory system medication items claimed during 2004 (N = 628 754). (Refer to table 5.7).

Anti-asthmatic medicine items contributed 28.54% (N = 44 201) of all asthma-related medicine items claimed during 2004. The anti-asthmatic medicine items represented 34.92% (R10 324 664.94) of the total cost of all the asthma-related medication (N=R 29 567 363.00). (Refer to tables 5.7 and 5.8). Tables 5.6 and 5.7 indicate the prevalence of the asthma-related medication. It also indicates that the prevalence of both bronchodilators and anti-asthmatics was more or less the same between the different three-month study periods, with only a slight decrease during the months May to August. Table 5.8 displays the prevalence and cost representation of the bronchodilators during the three study periods in 2004.

Table 5.8 The bronchodilator medicine usage and cost for the period 1 January to the 31 December 2004

Study period	Total cost of bronchodilator medication (R)	Total cost of all medicine items (%)	Total cost of all respiratory system agents (%)	Average cost of all bronchodilators per item (R)
January to April	R 6 276 489.22	3.15 (N=R 198 934 122)	43.00 (N=R14 594 715.28)	R213.94 (± R250.34) (N=29 337)
May to August	R 6 996 191.50	2.88 (N=R 242 721 616)	33.75 (N=R20 730 622.72)	R 172.15 (± R308.76) (N= 40 641)
September to December	R 5 970 017.34	2.72 (N=R 219 567 408)	40.54 (N=R14 724 675.28)	R 146.78 (± R150.13) (N= 40 672)
Average: Jan - Dec	**R 19 242 698.06**	**2.91 (N=R 661 223 146)**	**38.45 (N=R50 050 013.28)**	**R173.91 (± R246.20) (N=110 650)**

From 1 January to 31 December 2004, the bronchodilators contributed 71.46% (N = 110 650) of all asthma-related medicine items (N = 154 851). During this period the total cost of the bronchodilators amounted to R 19 242 698.06 (table 5.8) and represented 65.08% of all asthma-related medications (N = R 29 567 363.00). The period of September to December had the highest percentage prevalence for the year 2004. Though the total cost of anti-asthma medicine was the highest during the months May to August. As with the anti-asthmatics, the bronchodilators also showed a reduction on the average cost per medicine item. The reduction in average cost for bronchodilators per medicine item was approximately R 67 for the study period of 2004. (Refer to table 5.8).

Table 5.9 displays the prevalence and cost representation of the anti-asthmatics during the three-month study periods.

Table 5.9 The anti-asthmatic medicine usage and cost for the period 1 January to the 31 December 2004

Study period	Total cost of anti-asthmatic medicine items (R)	Total cost all medicine items (%)	Total cost of all respiratory system agents (%)	Average cost of anti-asthmatic medicine items (R)
January to April	R 2 946 940.65	1.48 (N=R198 934 122)	20.19 (N=R14 594 715.28)	R 267.85 (± R 143.34) (N=11 002)
May to August	R 3 642 986.63	1.50 (N= R 242 721 616)	17.57 (N=R20 730 622.72)	R 240.00 (± R 118.70) (N=15 179)
September to December	R 3 734 737.66	1.70 (N= R 219 567 408)	25.36 (N=R14 724 675.28)	R 207.26 (± R 93.79) (N= 18 020)
Average: Jan -Dec	**R 10 324664.94**	**1.56 (N= R 661 223 146)**	**20.63 (N=R50 050 013.28)**	**R 233.58 (± R118.86) (N=44 201**

The period of September to December had the highest percentage prevalence for anti-asthmatics and also the highest total cost value during 2004. The reduction in average cost per item is the possible effect of the new pricing regulation.

A price reduction of approximately R 60 was recorded for the year (d-values calculated in section 5.9.1). (Refer to table 5.9)

5.4 COST PREVALENCE INDEX

The cost prevalence index of the total database and the respiratory system will be calculated and discussed.

5.4.1 COST PREVALENCE INDEX OF THE MEDICINE CLAIMS DATABASE VS. ASTHMA-RELATED MEDICINE

The cost prevalence indices (CPI) may be used to compare relatively expensive medication (bronchodilators and anti-asthmatic medication) vs. medication in the database by using cost and prevalence percentages. The calculated cost prevalence index may be used as an instrument to describe different medicine treatments as relatively expensive or inexpensive.

Table 5.10 Comparing the usage and cost of bronchodilators with total medicine claims database

Study period	Cost as % of the total database (%)	Prevalence (items) as % of total database (%)	Cost prevalence Index
January to April	3.15 (N= R 198 934 122)	2.15 (N = 1 363 585)	1.47
May to August	2.88 (N= R 242 721 616)	2.08 (N = 1 953 845)	1.38
September to December	2.72 (N= R 219 567 408)	2.05 (N = 1 988 452)	1.33
Jan-Dec Average:	**2.91 (N= R 661 223 146)**	**2.09 (N= 5 305 882)**	**1.39**

Table 5.11 Comparing the usage and cost of anti-asthmatics with total medicine claims database.

Timeframe	Cost as % of the total database (%)	Prevalence (items) as % of total database (%)	Cost prevalence Index
January to April	1.48 (N= R198 934 122)	0.81 (N = 1 363 585)	1.82
May to August	1.50 (N= R242 721 616)	0.78 (N = 1 953 845)	1.92
September to December	1.70 (N= R219 567 408)	0.91 (N=1 988 452)	1.86
Jan- Dec Average:	**1.56 (N= R 661 223 146)**	**0.83 (N= 5 305 882)**	**1.88**

As seen in table 5.10 and table 5.11 the CPI calculated for bronchodilators and anti-asthmatic medication is more than 1 for all three the four-month study periods. This indicates that these medications, the bronchodilators (average = 1.39) and the anti-asthmatics (average = 1.88), were relatively expensive in comparison with other treatments. The CPI for the bronchodilators showed a slight decrease from January to April, to September to December and the CPI of the anti-asthmatics showed an increase.

5.4.2 COST PREVALENCE INDEX OF THE RESPIRATORY SYSTEM MEDICINE VS. ASTHMA-RELATED MEDICINE

The results in table 5.12 reveal that the CPI of the bronchodilators for the different four-month periods are all more than one, this indicates that these asthma-related medications are relatively expensive.

Table 5.12 Comparing the usage and cost of bronchodilators with respiratory system medicine (January to December 2004)

Timeframe	Cost as % of Respiratory system medication (%)	Prevalence as% of Respiratory system medication (%)	Cost prevalence Index
January to April 2004	43.00 (N= R 14 594 715.28)	20.54 (N =142 835)	2.09
May to August 2004	33.75 (N=R 20 730 622.72)	14.18 (N =286 615)	2.38
September to December 2004	40.54 (N= R 14 724 675.28)	20.40 (N =199 304)	1.99
Jan- Dec Average:	**38.45 (N= R50 050 013.28)**	**17.60 (N= 628 754)**	**2.18**

Table 5.13 Comparing the usage and cost of anti-asthmatics with respiratory system medicine

Timeframe	Cost as % of the Respiratory system medication (%)	Prevalence as % of Respiratory system medication (%)	Cost prevalence Index
January to April	20.19 (N = R 14 594 715.28)	7.70 (N =142835)	2.62
May to August	17.57 (N =R 20 730 622.72)	5.30 (N =286615)	3.31
September to December	25.36 (N = R 14 724 675.28)	9.04 (N =199304)	2.81
Weighted average:	**20.63 (N = R50 050 013.28)**	**7.03**	**2.93**

As seen in table 5.13, the CPI values calculated for anti-asthmatic medication as percentage of respiratory system medication are almost three, which indicates that the anti-asthmatics are relatively much more expensive than the other medications prescribed and claimed for the respiratory system.

5.4.3 Cost prevalence index of asthma-related medication

The CPI was done for asthma-related medication to evaluate the relative values of the bronchodilators vs. the anti-asthmatic medication.

Table 5.14 Comparing the usage and cost of bronchodilators with the asthma-related medication for 2004.

Timeframe	Cost as % of the asthma-related medication (%)	Prevalence as % of asthma-related medication (%)	Cost prevalence Index
January to April	68.04 (N= R 9 223 429.87)	72.73 (N= 40 339)	0.94
May to August	65.76 (N= R 10 639 178.13)	72.81 (N= 55 820)	0.90
September to December	61.52 (N= R9 704 755.00)	69.30 (N= 58 692)	0.89
Total:	**65.08 (N=29 567 363.00)**	**71.46 (N= 154 851)**	**0.91**

The CPI values of the bronchodilators calculated below one, indicating that they are relatively less expensive than the other anti-asthmatic groups. The condition or the severity of the patient's sickness normally determines the treatment of the patient, but the cost factor could also be argued to be one of the reasons why bronchodilators have a higher prevalence.

Table 5.15 Comparing the usage and cost of anti-asthmatics with the asthma-related medication for 2004.

Timeframe	Cost as % of the asthma-related medication (%)	Prevalence as % of asthma-related medication (%)	Cost prevalence Index
January to April	31.95 (N= R 9 223 429.87)	27.27 (N= 40 339)	1.17
May to August	34.24 (N= R 10 639 178.13)	27.19 (N= 55 820)	1.26
September to December	38.48 (N= R9 704 755.00)	30.70 (N= 58 692)	1.25
Total:	**34.92 (N= R29 567 363.00)**	**28.54 (N= 154 851)**	**1.22**

It is clear that the anti-asthmatics are the more expensive treatment for asthma. They are not only more expensive than the bronchodilators but also, as illustrated in table 5.8 and in table 5.10, relatively more expensive than the other medications in the database. The most effective treatment should always be the first choice, but the affordability of the anti-asthmatics by patients could be one of the reasons why bronchodilators have a higher prevalence.

5.5 ASPECTS OF COMPARING PREVALENCE OF ASTHMA MEDICATION 1995 VS. 2004

To determine whether there was a change in the prevalence of asthma-related medication used, the results of this study were compared with the results of a previous study.

A study done by Serfontein (1996) regarding medicine usage, showed the following information on asthma-related medicine prevalence:

Data from the 1 January 1995 to the 30 June 1995 have been used for the asthma usage analysis (Serfontein, 1996: 119). Table 5.16 shows the number of prescriptions dispensed during the six-month period as well as the number of asthma prescriptions, the total cost and the average cost of the prescriptions.

Table 5.16 The prevalence of asthma medication according to number of prescriptions and cost in 1995 (Serfontein, 1996, 118).

Description	Total patients	Asthma patients
Number of patients	29000	3534
Number of prescription	132 264	27 071
Total cost	R 23 027 505.22	R 5 463 197.48
Average cost	R 174.10	R 216.24
Standard deviation	R 19.03	R 28.03

From tables 5.1, 5.2 and 5.16 it can be deduced that the average cost of medication per prescription was lower in 1995 than in 2004 (R255.59).

Serfontein concluded that prescriptions for asthma-related medication represented 20.47% of the total number of prescriptions and 23.72% of the total cost of the prescriptions dispensed during the six-month period (Table 5.16). It would thus seem that 12.19% of the asthma patients represented in the database were responsible for nearly 24% of the total cost (total population) (Serfontein, 1996: 119).

Table 5.17 represents a comparison between the two study periods 1995 and 2004..

Table 5.17 Percentage prevalence and cost of 1995 vs. 2004

Study year	Cost (%)	Prevalence (Prescriptions) (%)	Asthma prescriptions/patients
1995	23.72 (N=R5 463197.48)	20.47 (N= 27 071)	27 071 / 3 534*
2004	4.47 (N=R 29 567 363)	4.46 (N= 115 684)	115 684**

*In Serfontein's study, 3 534 patients used 27071 prescriptions in the study period.

**For this study a patient and a prescription were viewed as synonymous.

CPI 1995:

$$\text{CPI} = \frac{\%\,\text{cost}}{\%\,prevalence(prescriptions)}$$

$$= \frac{23.72\%}{20.47\%}$$

$$= 1.16$$

The CPI value for 1995 indicates that the asthma treatment per prescription utilised was slightly more expensive than the rest of the medicines claimed according to the database, as it has a value greater than one.

CPI 2004:

$$CPI = \frac{\%\cos t}{\%\, prevalence(\Pr escriptions)}$$

$$= \frac{4.47\%}{4.45\%}$$

$$= 1.00$$

If cost index = 1: equilibrium exists between the cost and the prevalence of prescriptions of the asthma therapy.

A slight decrease in the CPI from 1995 to 2004 indicates that the therapy utilised for treatment of asthma was relatively less expensive in 2004 than in 1995 in comparison with the total database. This could be due to the influence of the new medicine pricing regulations or due to more generic medicine items being prescribed.

Table 5.18 A percentage comparison of the prevalence of innovator and generic asthma medicine

Study period	Generic medicine (%)	Innovator medicine(%)
1995 asthma medicine	20.72	79.28
(N=27 071)	(N=5 610)	(N=21461)
2004 asthma medicine	24.14	75.18
(N=132 567)*	(N=32 050)	(N=100 517)

*No combination medicine was included in this calculation

According to table 5.18 a slight increase in the prevalence of generic medicine for asthma treatment could be noticed. Serfontein reported in his study that out of the seven asthma medicine groups (as in table 5.19) only four had generic equivalents available (Serfontein, 1996: 156). During 2004 only the leukotriene receptor antagonists had no generic substitution. This medicine group was not documented in Serfontein's study.

Serfontein summarised in his study the total number of drugs used for the treatment of asthma as in table 5.19.

Table 5.19 Total number of drugs used for the treatment of asthma during 1995 (Serfontein, 1996: 119).

Therapeutic category	Number of prescriptions	Prevalence of database (N=26 347) (%)
Anti-allergic	1 007	3.62
Anti-cholinergic	2 693	10.22
Inhalation beta-agonists	8 094	30.72
Inhalation steroid	4 753	18.04
Long-acting beta-agonist	1 164	4.42
Methylxanthine therapy	6 221	23.61
Oral steroids	2 469	9.37
Total	**26 347**	**100**

In Serfontein's study prescriptions and items were viewed as synonyms. To compare the prevalence of the therapeutic groups from the two study periods the prevalence of the inhalation steroids and oral steroids was combined. Inhalation beta-agonists were also viewed as short acting beta agonists. In Serfontein's study leukotriene inhibitors were not included.

From table 5.20 the difference in prevalence of the asthma medicine to the respective databases can be viewed. A decrease in the prevalence of anti-allergic anticholinergic and the methylxanthine medicine could be noticed. The anticholinergic medicine had the highest percentage decrease of 7.53%. An increase of 7.41% in the usage of corticosteroids was recorded. The beta-agonists also showed a small decrease in prevalence.

Table 5.20 Summary of the total number of drugs used for the treatment of asthma during the study period 1995 vs. 2004

Study period	1995		2004	
Therapeutic category	Number of prescriptions	Prevalence of database (N=26 347) (%)	Number of items	Prevalence of asthma medication (N=154 851) (%)
Anti-allergic	1 007	3.62	2 076	1.34
Anticholinergic	2 693	10.22	4 170	2.69
Short acting selective $beta_2$-agonists	8 094	30.72	40 789	26.34
Leukotriene inhibitor	n/a	n/a	5 395	3.48
Long-acting beta-agonist	1 164	4.42	5 602	3.62
Methylxanthines	6 221	23.61	19 281	12.46
Corticosteroids	7 222	27.41	53 925	34.82
Combination therapy	n/a	n/a	23 613	15.25
Total	**26 347**	**100**	**154 851**	**100**

5.6 THE RELEVANCE AND FREQUENCY OF GENERIC SUBSTITUTION OF THE DIFFERENT CATEGORIES OF ANTI-ASTHMA MEDICATION.

A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, and route of administration, quality, performance characteristics and intended use (FDA/Centre for Drug Evaluation and Research, 2005). Table 5.21 indicates the prevalence of innovator and generic medication for each of the pharmacological groups during the study period 2004.

Table 5.21 The prevalence of innovator and generic asthma-related medication for the year 2004.

	Generic medication		*Innovator medication*	
Description	**Frequency**	**Prevalence (%)**	**Frequency**	**Prevalence (%)**
Sympathomimetics (N = 53 406)	23 921	44.79	29 485	55.21
Glucocorticoids (N = 24 626)	4 818	19.56	19 808	80.44
Methylxanthines (N = 22 659)	1 910	8.43	20 749	91.57
Combinations (N = 20 317)	-	0.00	20317	100.00
Other anti-asthmatics (N = 4 773)	374	7.84	4 399	92.16
Anticholinergics (N = 4 088)	493	12.06	3 595	87.94
Leukotriene receptor antagonists (N = 1 405)	-	0.00	1 405	100.00
Chromones (N = 1 293)	534	41.30	759	58.70
Total: (N = 132 567)	**32 050**	**24.18**	**100 517**	**75.82**

From table 5.21 it can be deduced that innovator anti-asthma products have a much higher prevalence than the generic products. Thus in asthma treatment, generic substitution is either not favoured by the prescribers for asthma patients or there are not so many generic products available on the South African market. There are also products like leukotriene receptor antagonists where no generic substitution was manufactured during the study period. On further investigation it was found that there is no generic medicine available for leukotriene receptor antagonists (MiMS®, 2003: 170).

In comparison with the total database (33.49%, N = 5 305 882), the generic substitution of asthma medication is far less, representing 24.18% of medication prescribed for asthma. As discussed in chapter 3, generic drug products that have been approved by the FDA (Food and Drug Administration) must meet the same rigorous standards for safety and effectiveness as brand-name drugs. The availability of generic drugs for asthma-related medication could be accountable for the higher prevalence in innovator medication.

In table 5.22 the prevalence of innovator medicine is illustrated for the different active ingredients in asthma-related medicine. Some of the medicine had no generic substitution available or the innovator medicine was preferred.

5.22 The prevalence of innovator medicine for the different active ingredients in asthma-related medicine for the period 2004.

Active ingredients	Prevalence of innovator medicine	Percentage prevalence (%)
1. *Salbutamol (N = 30 719)*	*6 799*	22.13
2. Budesonide (N = 23 997)	21 890	91.22
3. Theophylline (N = 19 008)	17 536	92.26
4. Fluticasone Propionate (N = 17 195)	17 195	100.00
5. Ipratropium/Salbutamol (N = 9 575)*	9 575	100.00
6. Fenoterol (N = 9 033)	9 033	100.00
7. Fenoterol/Ipratropium (N = 8 206)	8 206	100.00
8. Fluticasone (N = 7 070)	7 070	100.00
9. Beclomethesone (N = 5 663)	2 934	51.81
10. Montelukast (N = 5 284)	5 284	100.00
11. Salmetarol (N = 3 458)	*3 458*	100.00
12. Ipratropium (N = 2 688)	2 195	81.66
13. Theophyllin/Etophyllin (N = 2 643)*	2 643	100.00
14. Budesonide/Formoterol (N = 2 454)*	2 454	100.00
15. Formoterol (N = 2 144)	2 144	100.00
16. Ketotifen (N = 2 072)	1 168	56.37
17. Tiotropium (N = 1 482)	1 482	100.00
18. Terbutaline (N = 553)	553	100.00
19. Hexoprenaline (N = 484)	484	100.00
20. Aminophylline/Ephedrine (N = 413)*	0	0.00
21. Etafedrine/Ambuphullin (N = 309)*	309	100.00
22. Aminophylline (N = 273)	273	100.00
23. Zafirlukast (N =111)	111	111
24. Theophyllin/Ephedrine (N = 13)*	0	0.00
(N = 154851) Total:	**122 796**	**79.30**

*Combination medicine was included in this calculation

Table 5.23 The average cost of innovator and generic asthma medication for the three four-month periods 2004.

Study period	Generic: Average cost of asthma-related medication	Innovator: Average cost of asthma-related medication
January to April	R 52.62 (± R 53.36) (N = 8 120)	R 273.01 (± R 233.04) (N = 32 219)
May to August	R 49.68 (± R 49.25) (N = 12 049)	R 230.49 (± R 294.15) (N = 43 771)
September to December	R 41.33 (± R 48.86) (N = 11 881)	R 196.83 (± R 135.81) (N = 46 811)
Average:	***R 45.83*** **(± R 50.37)** **(N=32 050)**	***R 228.81*** **(± R 230.27)** **(N=122 801)**

Although the innovator medication had a cost reduction of 27.90% probably due to the new pricing regulation, it was still much more expensive than the generic medication (Refer to table 5.23). The generic medication also showed a cost reduction of 21.46%. The prevalence of the innovator medication was still much higher than that of the generic items. This is due to two facts; firstly that the high costs had no real effect on the prevalence of the innovator medicine and secondly that there were no generic substitutions available for certain medicines. According to the Congressional Budget Office in the USA, generic medication saves consumers an estimated $8 to $10 billion a year at retail pharmacies in America. Even more billions are saved when hospitals use generics (FDA/Centre for Drug Evaluation and Research, 2005).

Table 5.24 indicates the average cost of innovator and generic medicine for the three study periods during 2004. The effect of new pricing regulations pertaining to medicine is visible on the average cost of the medicine

Table 5.24 Average cost of innovator and generic anti-asthma medicine for the study period 2004.

Innovator / generic	Products	Average cost per item for January to April 2004	Average cost per item for May to August 2004	Average cost per item for September to December 2004	Average cost per item for January to December 2004
	Salbutamol				
Innovator	Ventolin® 200 INH (N=743)	R81.48 ±R21.25	R90.45 ±R36.73	R73.88 ±R42.00	R83.75 ±R39.21
	Ventolin® 300 INH (N=91)	R85.58 ±R25.95	R76.60 ±R37.65	R64.04 ±R30.41	R77.21 ±R32.20
	Ventolin® 200 Ref (N=196)	R92.89 ±R55.96	R86.24 ±R41.86	R43.91 ±R14.87	R80.27 ±R47.24
	Ventolin® Syr (N=118)	R35.81 ±R21.25	R50.81 ±28.33	R38.52 ±R30.89	R43.20 ±R28.23
	Ventolin® Resp Sol (N=34)	R93.05 ±R69.94	R116.50 ±R56.42	R118.82 ±R84.30	R110.57 ±R67.43
	Volmax® 4mg tab (N=116)	R160.99 ±R72.43	R144.59 ±R57.35	R115.63 ±R52.43	R138.96 ±R63.06
	Cybutol® 200 Cap (N=13)	R47.42 ±R0.45	R24.38 ±R1.12	R31.47 ±R9.97	R38.97 ±R11.00
Generic	Asthavent® M.D 200 INH (N=6 058)	R33.26 ±R10.18	R29.94 ±R13.28	R23.25 ±R21.16	R28.32 ±R11.16
	Venteze® Complete INH (N=9 710)	R34.68 ±R15.73	R30.44 ±R14.39	R34.47 ±R30.15	R29.40 ±R22.22
	Airomir® INH (N= 74)	R100.30 ±R36.88	R105.54 ±R34.27	R52.29 ±R32.39	R87.93 ±R39.54
	Asthavent® M.D 300 INH (N=1 492)	R45.19 ±R6.79	R38.04 ±R10.22	R30.82 ±R26.04	R36.58 ±R10.17
	Venteze® INH REF (N=443)	R34.63 ±R10.57	R27.34 ±R30.07	R5.05 ±R6.37	R26.48 ±R22.96
	Venteze® Syr (N=3 085)	R15.73 ±R8.38	R15.79 ±R7.09	R13.47 ±R11.29	R14.96 ±R7.58

Table 5.24 Continued

Innovator / generic	**Products**	**Average cost per item for January to April 2004**	**Average cost per item for May to August 2004**	**Average cost per item for September to December 2004**	**Average cost per item for January to December 2004**
	Venteze® Resp Sol (N = 121)	R43.78 ±R25.91	R40.14 ±R22.76	R28.77 ±R10.90	R38.61 ±R22.43
	Asthavent® Syr (N = 1 696)	R15.00 ±R9.21	R14.91 ±R5.43	R12.45 ±R6.64	R14.00 ±R6.74
	Venteze® 4mg Tab (N = 816)	R34.60 ±R25.16	R28.64 ±20.84	R23.61 ±R18.83	R27.84 ±R20.64
	Asthavent® DP CAP (N = 2)	R35.66 ±R24.17	-	-	R35.66 ±R24.17
	Theophyllin				
Innovator	Nuelin® liquid SYR (N = 604)	R38.06 ±R19.12	R34.47 ±R15.47	R29.04 ±R19.12	R33.69 ±R18.18
Generic	Alcophyllin® SYR (N =1 472)	R36.81 ±R10.76	R18.91 ±R13.85	R8.66 ±R4.74	R20.95 ±R15.39
	Ipratropium				
Innovator	Atrovent® 0.25mg UDV (N = 829)	R101.90 ±R95.43	R86.55 ±R74.63	R46.37 ±R38.32	R78.37 ±R75.96
	Atrovent® 0.5mg UDV (N = 483)	R224.33 ±R200.49	R167.12 ±R155.49	R103.20 ±R89.99	R166.99 ±R163.56
	Atrovent® 40 Inhalets (N = 7)	R173.89 ±R46.17	R167.28 ±R0.00	R112.22 ±R43.20	R146.52 ±R48.66
Genenric	Sabax® Ipratropium NI101 (N = 33)	R89.80 ±R40.05	R64.73 ±R26.64	R32.37 ±R10.41	R64.17 ±R32.75
	Sabax® Ipratropium NI201 (N = 15)	R257.08 ±R220.89	R139.49 ±R128.21	R150.74 ±R62.12	R175.35 ±R138.41
	Ipvent® 40 200D INH (N = 460)	R103.14 ±R31.44	R90.10 ±R17.14	R79.06 ±R15.38	R89.82 ±R23.34

Table 5.24 Continued

Innovator / generic	**Products**	**Average cost per item for January to April 2004**	**Average cost per item for May to August 2004**	**Average cost per item for September to December 2004**	**Average cost per item for January to December 2004**
	Beclomethasone				
Innovator	Becotide® 100 INH (N = 213)	R143.56 ±R21.06	R118.61 ±R19.33	R99.63 ±R3.74	R123.58 ±R24.99
	Becotide® 50 INH (N = 56)	R90.08 ±R44.31	R67.60 ±R9.67	R52.57 ±R10.74	R68.75 ±R28.83
	Aerobec® Forte Autohaler (N = 6)	R433.03 ±R49.19	-	R307.57 ±R0.00	R391.21 ±R7516
Generic	Beclate® 100mcg INH (N = 1 513)	R139.84 ±r19.03	R125.52 ±R19.11	R104.97 ±R6.03	R120.51 ±R20.64
	QVAR® INH 100 (N = 495)	R243.24 ±R92.31	R219.17 ±R55.92	R186.28 ±R41.72	R215.49 ±R69.07
	Beceze® 100mcg INH (N = 29)	R148.54 ±R18.21	R160.35 ±R98.91	R60.69 ±R64.51	R121.91 ±R79.41
	Beclate® 50mcg INH (N = 433)	R75.85 ±R14.96	R65.84 ±R11.42	R55.62 ±R7.29	R64.49 ±R13.68
	QVAR® 50 INH (N = 39)	R139.32 ±R30.96	R143.16 ±R16.67	R101.12 ±R35.66	R131.30 ±R31.66
	Beceze® 50mcg INH (N = 3)	R80.48 ±R0.00	R80.63 ±R0.00	-	R80.58 ±R0.09
	Ventzone® INH (N = 2)	R108.51 ±R0.00	R108.51 ±R0.00	-	R108.51 ±R0.00
	Clenil® Aerosol INH (N =116)	R79.43 ±R6.51	R52.05 ±R8.92	R46.59 ±R1.82	R59.51 ±R15.93
	Beceze® 250mcg INH (N = 22	R257.24 ±R0.83	R270.18 ±R0.00	R240.54 ±R0.00	R256.04 ±R12.15

Table 5.24 Continued

Innovator / generic	Products	Average cost per item for January to April 2004	Average cost per item for May to August 2004	Average cost per item for September to December 2004	Average cost per item for January to December 2004
	Budesonide				
Innovator	Inflammide® 200 Mac (N = 5 689)	R236.91 ±R34.52	R217.73 ±R27.30	R182.06 ±R15.74	R205.65 ±R33.64
	Inflammide® 100 Mac (N = 2 224)	R169.06 ±R19.74	R156.31 ±R23.94	R137.79 ±R7.59	R150.93 ±R21.52
	Pulmicort® 100ug INH (N = 485)	R189.19 ±R29.79	R177.90 ±R25.05	R148.02 ±R23.05	R169.16 ±R30.79
Generic	Budeflam® MET 200mcg (N = 7)	R161.20 ±R9.36	R174.72 ±R0.00	-	R168.93 ±R9.02
	Budeflam® MET 100mcg (N = 7)	R154.00 ±R0.55	-	-	R154.00 ±R0.55
	Budeflam® 100/300 GEN (N = 2 055)	R177.59 ±R21.51	R175.00 ±R14.67	R160.30 ±R10.68	R169.04 ±R16.93
	Ketotifen				
Innovator	Ketohexal® 200ml SYR (N = 409)	R67.82 ±R19.75	R62.43 ±R16.60	R56.19 ±R12.86	R61.08 ±R16.62
Generic	Zetofen® 200ml SYR (N = 534)	R74.77 ±R22.83	R68.39 ±R17.73	R54.80 ±R14.62	R64.46 ±R19.76
	ADCO-Ketotifen SYR (N = 374)	R50.22 ±R34.66	R60.54 ±R19.81	R57.10 ±R22.29	R56.91 ±R24.97

The generic substitution for all the innovator medicine is illustrated in the appendix.

The total saving for substituting the innovator/original medicine for 2004 can be calculated from table 5.24. If the innovator drug could be substituted by the generic product with lowest average cost, the total saving would be R 352 679.25. This is calculated when the prevalence of the innovator drug is multiplied with the generic product's average cost and adding it up.

Table 5.25 The percentage prevalence distribution of generic and innovator medicine for the study period of 2004.

Study period	Generic: Percentage prevalence of asthma medication (%)	Percentage prevalence of total database (%)	Innovator: Percentage prevalence of asthma medication (%)	Percentage prevalence of total database (%)
January to April **(N= 40 339)**	20.13 (N = 8 120)	0.60 (N = 1 363 585)	79.87 (N = 32 219)	2.36 (N = 1 363 585)
May to August (N= 55 820)	21.59 (N = 12 049)	0.62 (N = 1 953 845)	78.41 (N = 43 771)	2.24 (N = 1 953 845)
September to December (N= 58 692)	20.24 (N = 11 881)	0.60 (N = 1 988 452)	79.76 (N = 46 811)	2.35 (N = 1 988 452)
Total: January to December (N= 154 851)	**20.69 (N = 32 050)**	**0.60 (N 5 305 882)**	**79.30 (N = 122 801)**	**2.31 (N = 5 305 882)**

According to the results in table 5.25 the percentage prevalence of the innovator medication for asthma was much higher than that of the generic substitutions. According to these results the percentage prevalence of the innovator and generic medication through the three study periods, indicated in table 5.25, stayed relatively constant. This is emphasised by the percentage prevalence of the total database where the values were also more or less the same throughout the three study periods.

5.7 PREVALENCE AND COST OF ASTHMA TREATMENT ACCORDING TO ACTIVE INGREDIENTS

From the data obtained, the following are the active ingredients of asthma-related medicine claimed during the study period as illustrated in table 5.26. The prevalence of these active ingredients is also illustrated for the study period.

Table 5.26 The prevalence percentages of anti-asthmatic active ingredients for 2004.

Active Ingredients	*Prevalence of active ingredient/ items*	*Percentage prevalence of active ingredients* (N = 154 851) (%)
1. *Salbutamol*	30 719	*19.84*
2. Budesonide	23 997	15.50
3. Theophylline	19 008	12.28
4. Fluticasone Propionate	17 195	11.10
5. Ipratropium/Salbutamol	9 575	6.18
6. Fenoterol	9 033	5.83
7. Fenoterol/Ipratropium	8 206	5.30
8. Fluticasone	7 070	4.57
9. Beclomethesone	5 663	3.66
10. Montelukast	5 284	3.41
11. Salmetarol	3 485	*2.23*
12. Ipratropium	2 688	1.74
13. Theophyllin/Etophyllin	2 643	1.70
14. Budesonide/Formoterol	2 454	1.58
15. Formoterol	2 144	1.38
16. Ketotifen	2 076	1.34
17. Tiotropium	1 482	0.96
18. Terbutaline	553	0.36
19. Hexoprenaline	484	0.31
20. Aminophylline/Ephedrine	413	0.27
21. Etafedrine/Ambuphullin	309	0.20
22. Aminophylline	273	0.18
23. Zafirlukast	111	0.05
24. Theophyllin/Ephedrine	13	0.01

The active ingredients listed in table 5.26 can be classified as based in the MiMS® under the headings of 10.2 and 10.4.

Table 5.27 Short-acting selective β_2 agonists (MiMS® April 2004)

Active ingredients	**Number of items**	**Percentage prevalence (N=40 789) (%)**
Salbutamol	30 719	75.31
Fenoterol	9 033	22.15
Terbutaline	553	1.36
Hexoprenaline	484	1.19
	40 789	**100**

Table 5.28 Long-acting selective β_2 agonists (MiMS® April 2004)

Active ingredients	**Number of items**	**Percentage prevalence (N=5 602) (%)**
Salmeterol	3 458	61.73
Formoterol	2 144	38.27
	5 602	**100**

Table 5.29 Corticosteroids (MiMS® April 2004)

Active ingredients	**Number of items**	**Percentage prevalence (N=53 925) (%)**
Budesonide	23 997	44.50
Fluticasone propionate	17 195	31.89
Fluticasone	7 070	13.11
Beclomethesone	5 663	10.50
	53 925	**100**

Table 5.30 Anticholinergics (MiMS® April 2004)

Active ingredients	**Number of items**	**Percentage prevalence (N=4 170) (%)**
Tiotropium	1 482	35.54
Ipratropium	2 688	64.46
	4 170	**100**

Table 5.31 Methylxanthines (MiMS® April 2004)

Active ingredients	Number of items	Percentage prevalence (N=19 281) (%)
Theophylline	19 008	98.58
Aminophylline	273	1.42
Total	**19 281**	**100**

Table 5.32 Leukotriene Inhibitor (MiMS® April 2004)

Active ingredients	Number of items	Percentage prevalence (N=5 367) (%)
Montelukast	5 284	98.45
Zafirlukast	111	1.55
Total	**5 395**	**100**

Table 5.33 Anti-allergic drugs (MiMS® April 2004)

Active ingredients	Number of items	Percentage prevalence (N=2 076) (%)
Ketotifen*	2 076	100
Total	**100**	**100**

*Ketotifen has antihistaminic properties and a stabilising effect on mast cells (South African Medical Formulary, 2003: 494)

It is clear from tables 5.26, 5.28 and 5.29 that salbutamol (β_2-agonist) and Budesonide (corticosteroids) had a much higher prevalence than the rest of the asthma-related medicine. It could be that these medicines in combination may well be the preferred treatment for asthma according to the standard treatment guidelines and essential drug list (Department of health, 2003:196).

Table 5.34 indicates the percentage prevalence of combination therapy for asthma treatment. These combinations include different active ingredients presented in one dosage form.

Table 5.34 Asthma combination medicine (MiMS® April 2004)

Active ingredient combinations	Number of items	Percentage prevalence (N=23 613) (%)
Ipratropium/Salbutamol	9 575	40.55
Fenoterol/Ipratropium	8 206	34.75
Theophyllin/Etophyllin	2 643	11.19
Budesonide/Formoterol	2 454	10.39
Aminophylline/Ephedrine	413	1.75
Etafedrine/Ambuphullin	309	1.31
Theophyllin/Ephadrine	13	0.06
Total	**23 613**	**100**

It could be argued that the high frequency of salbutamol may be due to factors such as the following:

- Its effective mechanism of action in the treatment of asthma-related symptoms.
- The cost factor for the prescribers and patients.
- Safety and limited side-effects of the drug.
- Dosage forms (Sizes of inhalants)
- Availability of the products

To illustrate that the cost of drugs may have an effect on their usage, the five anti-asthmatic products with highest percentage prevalence will be used as an example. These items represent 64.9% of the anti-asthmatic medication used for 2004 (Refer to table 5.26). These anti-asthmatic active ingredients include salbutamol (19.84%), budesonide (15.50%), theophylline, (12.28%); fluticasone propionate (11.10%) and the combination of ipratropium/salputamol (6.18%) .The trade names of salbutamol are illustrated in table 5.35.

Table 5.35 Trade names with the highest prevalence of the active ingredient salbutamol medicine.

Description	Number of items	Percentage prevalence of salbutamol (N= 30 719) (%)
Venteze® Complete inhaler	9 710	31.61
Asthavent® M.D 200 Inhaler	6 058	19.72
Ventolin® Inhaler 200	3 565	11.61
Venteze® Syr	3 085	10.04
Asthavent® Syr	1 696	5.52
Asthavent® M.D. 300 Inhaler	1 492	4.86
Ventolin® Accuh Inhaler	1 311	4.27
Venteze® 4mg Tab	816	2.66
Ventolin® 200 Inhaler	743	2.42
Venteze inhaler Ref	443	1.44
Venteze® 2mg Tab	423	1.38
Ventolin® 200 Ref	196	0.64
Ventolin® 300 Ref	179	0.58
Ventolin® 2.5 Nebules	166	0.54
Venteze® Respiratory solution	121	0.39
Ventolin® Syr	117	0.38
Volmax® 4mg Tab	116	0.38
Volmax® 8mg Tab	102	0.33
Ventolin® 300 Inhaler	91	0.30
Airomir® Inhaler	74	0.24
Ventolin® 5mg Nebules	64	0.21
Salbulin® Autohaler	59	0.19
Ventolin® Respiratory solution	34	0.11
Cybutol® 400 Caps	27	0.09
Cybutol® 200 Caps	13	0.04
Ventodisk® 400mcg	10	0.03
Ventolin® Diskhaler	3	0.01
Asthavent® DP Cap	2	0.01
Venteze® ECO Met Dose	1	0.00
Ventolin® 4mg Tab	1	0.00
Total:	**30 719**	**100**

Table 5.36 Average cost of salbutamol medicine for the study period 2004.

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Venteze® Complete inhaler	R34.68 ±R15.73	R30.44 ±R1439	R24.47 ±R30.15	R29.40 ±R22.21
Asthavent® M.D 200 Inhaler	R33.26 ±R10.18	R29.97 ±R13.25	R23.25 ±R6.69	R28.32 ±R11.16
Ventolin® Inhaler 200	R86.58 ±R40.54	R90.45 ±R36.73	R57.87 ±R20.40	R70.77 ±R30.91
Venteze® Syr	R15.73 ±R8.38	R15.79 ±R10.22	R13.47 ±R7.34	R14.96 ±R7.58
Asthavent® Syr	R15.00 ±R9.22	R14.92 ±R5.43	R12.45 ±R6.64	R14.00 ±R6.74
Asthavent® M.D. 300 Inhaler	R45.18 ±R6.79	R38.04 ±R10.22	R30.82 ±R7.67	R36.58 ±R10.17
Ventolin® Accuh Inhaler	R115.62 ±R16.56	R107.93 ±R17.40	R107.60 ±R12.44	R109.87 ±R15.78
Venteze® 4mg Tab	R34.60 ±R25.16	R28.64 ±R20.84	R23.61 ±R16.55	R27.84 ±R20.64
Ventolin® 200 Inhaler	R81.48 ±R38.36	R93.46 ±R26.22	R73.88 ±R42.00	R83.75 ±R39.21
Venteze inhaler Ref	R34.63 ±R10.57	R27.34 ±R30.07	R5.05 ±R6.37	R26.47 ±R22.96
Venteze® 2mg Tab	R24.96 ±R18.25	R18.29 ±R11.98	R15.73 ± R12.68	R18.25 ±R13.67
Ventolin® 200 Ref	R92.89 ±R55.96	R86.24 ±R41.86	R43.91 ±R14.87	R80.27 ±R47.24
Ventolin® 300 Ref	R86.61 ±R32.32	R59.27 ±R22.67	R49.62 ±R21.11	R74.10 ±R32.63
Ventolin® 2.5 Nebules	R95.09 ±R70.39	R132.06 ±R108.06	R80.87 ±R83.40	R104.10 ±R92.45
Venteze® Respiratory solution	R43.78 ±R25.91	R40.14 ±R22.76	R28.77 ±R10.90	R110.57 ±R67.43
Ventolin® Syr	R35.81 ±R21.25	R50.81 ±R28.33	R38.52 ±R30.89	R43.20 ±R28.23

Table 5.36 Continued

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Volmax® 4mg Tab	R161.00 ±R75.93	R144.59 ±R57.35	R115.63 ±R52.43	R138.96 ±R63.06
Volmax® 8mg Tab	R212.87 ±R 72.43	R170.92 ±R78.48	R131.79 ±R67.73	R178.55 ±R79.56
Ventolin® 300 Inhaler	R85.58 ±R25.95	R76.60 ±R37.65	R64.04 ±R30.41	R77.31 ±R32.20
Airomir® Inhaler	R100.30 ±R36.88	R105.54 ±R34.27	R52.29 ±R22.67	R87.93 ±R39.54
Ventolin® 5mg Nebules	R93.05 ±R69.94	R81.73 ±R87.93	R151.28 ±R58.80	R103.41 ±R82.25
Salbulin® Autohaler	R180.80 ±R 20.08	R162.42 ±R27.67	R159.44 ±R8.14	R168.00 ±R22.15
Ventolin® Respiratory solution	R105.95 ±R 72.20	R116.50 ±R56.42	R118.82 ±R84.31	R38.61 ±R22.43
Cybutol® 400 Caps	R71.07 ±R17.96	R71.18 ±R59.39	R43.84 ±R12.30	R64.04 ±R25.02
Cybutol® 200 Caps	R47.42 ±R 0.45	R24.38 ±R1.12	R31.47 ±R9.97	R38.97 ±R11.00
Ventodisk® 400mcg	R189.63 ±R 1.67	R200.13 ±R0.00	R184.93 ±R0.00	R191.95 ±R7.29
Ventolin® Diskhaler	R72.62 ±R 0.00	-	-	R72.62 ±R0.00
Asthavent® DP Cap	R35.66 ±R24.17	-	-	R35.66 ±R24.17
Venteze® ECO Met Dose	-	-	R33.55 ±R0.00	R33.55 ±R0.00
Ventolin® 4mg Tab	-	R16.05 ±R0.00	-	R16.08 ±R0.00

Table 5.37 Average cost of budesonide medicine for the study period 2004.

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Budeflam® 100/300 ZER	R252.06 ±R0.00	-	-	R252.05 ±R0.00
Budeflam® 100mcg 300	R145.81 ±R0.00	R152.87 ±R0.00	-	R149.34 ±R4.99
Budeflam® 200/300 GEN	R235.83 ±R46.77	R238.40 ±R19.63	R215.84 ±R11.71	R227.64 ±R28.24
Budeflam® 200/300 ZER	-	R287.90 ±R0.00	R254.60 ±R0.00	R271.25 ±R19.23
Budeflam® 200mcg 300	-	R212.25 ±R0.00	R194.55 ±R0.00	R200.45 ±R10.22
Inflacor® 400mcg CPS	R177.10 ±R0.00	R120.49 ±R74.78	R146.72 ±R0.00	R141.35 ±R41.70
Inflammide® INH	-		R172.68 ±R0.00	R172.68 ±R0.00
Inflammide® 100 I/SYS	R363.42 ±R59.45	R341.64 ±R46.18	R281.74 ±R275.72	R320.70 ±R55.10
Inflammide® 100 MAC	R169.06 ±R19.74	R156.31 ±R23.94	R137.79 ±R7.59	R150.93 ±R21.52
Inflammide® 200 I/SYS	R481.95 ±R64.55	R446.96 ±R35.45	R343.98 ±R15.20	R380.30 ±R61.55
Inflammide® 200 MAC	R236.91 ±R34.52	R217.73 ±R27.30	R182.06 ±R15.74	R205.64 ±R33.64
Inflammide® 50 MAC	R124.02 ±R17.72	R116.76 ±R12.27	R102.86 ±R9.80	R112.62 ±R138.85
Pulmicort® 0.25mg UDV	R150.68 ±R105.37	R148.58 ±R101.65	R119.51 ±R97.73	R189.02 ±R176.69
Pulmicort® 0.5mg UDV	R207.63 ±R216.80	R176.26 ±R155.08	R91.60 ±R169.42	R189.02 ±R176.69
Pulmicort® 100ug INH	R189.19 ±R29.79	R177.90 ±R25.08	R148.02 ±R23.05	R169.16 ±R30.80

Tanle 5.37 Continued

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Pulmicort® 50ug INH	R108.30 ±R50.01	R112.22 ±R16.25	R84.86 ±R27.47	R100.57 ±R34.98
Pulmicort® TUR 400/50	R369.80 ±R150.81	R253.99 ±R130.39	R171.58 ±R10.52	R222.87 ±R110.18
Pulmicort® 400/100	R526.35 ±R167.68	R434.68 ±R107.03	R336.54 ±R88.18	R419.96 ±R139.83
Pulmicort® Turbo 100	R234.74 ±R27.95	R216.36 ±R46.63	R174.00 ±R24.59	R204.69 ±R42.67
Pulmicort® Turbo 200	R482.52 ±R70.25	R424.90 ±R57.58	R324.76 ±R47.44	R407.07 ±R88.21
Budeflam® 100/300 Gen	R177.59 ±R21.51	R175.00 ±R14.67	R160.28 ±R10.68	R169.04 ±R16.93
Budeflam® 200mcg+ZERO	-	-	R43.61 ±R0.00	R43.61 ±R0.00
Budeflam® MET 100mcg	R154.00 ±R0.55	-	-	R154.00 ±R0.55
Budeflam® MET 200mcg	R161.20 ±R9.36	R174.72 ±R0.00	-	R168.93 ±R9.02
Inflacor® 200mcg CAPS	R99.07 ±R50.71	R76.01 ±R32.43	-	R93.00 ±R46.90

Table 5.38 Average cost of theophylline medicine for the study period 2004.

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Chronophyllin ® 250CAP	R145.42 ±R0.00	R152.46 ±R0.00	R147.12 ±R0.00	R148.63 ±R2.88
Chronophyllin ® 375CAP	R203.83 ±30.91	R284.28 ±R61.31	R266.54 ±R45.88	R254.35 ±R57.10
Euphyllin® Retard TAB	R170.00 ±R59.02	R148.36 ±R49.12	R129.96 ±R42.02	R147.40 ±R52.28
Microphyllin® 125 CAP	R174.79 ±R58.34	R143.24 ±R49.13	R129.65 ±R50.80	R147.31 ±R55.36
Microphyllin® 250 CAP	R276.35 ±R77.92	R208.21 ±R66.23	R166.36 ±R53.11	R213.57 ±R79.40
Nuelin® 125mg TAB	R148.31 ±R142.47	R109.46 ±R26.20	R73.70 ±R45.20	R106.67 ±R87.45
Nuelin® Liquid SYR	R38.06 ±R19.12	R34.47 ±R15.47	R29.04 ±R19.12	R33.69 ±R18.18
Nuelin® SA 250 mg TAB	R152.75 ±R50.56	R129.45 ±R58.34	R111.67 ±39.26	R127.57 ±R51.91
Nuelin® SA 200mg TAB	R95.94 ±R55.24	R149.14 ±R67.47	R111.35 ±R42.38	R120.88 ±R57.11
Nuelin® SA 300mg TAB	R215.27 ±R22.01	R168.40 ±R83.51	R179.82 ±R2.58	R188.67 ±R60.68
Pylmophyllin® SR 200	R90.27 ±R0.00	R90.48 ±R41.72	R56.36 ±R22.50	R73.37 ±R28.22
Pylmophyllin® SR 300	R104.02 ±R45.05	R56.15 ±R42.00	R25.89 ±R11.24	R55.92 ±R45.49
Rolab-Theophyllin® SR	R101.26 ±R48.01	R63.50 ±R42.60	R42.44 ±R21.34	R73.51 ±47.37
SANDOZ Theophyllin SR	-	-	R39.51 ±R15.53	R39.51 ±R15.53
Theo-dur® 200mg TAB	R148.21 ±R78.78	R171.24 ±R0.00	-	R151.07 ±R73.39

Table 5.38 Continued

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Theophen® ELIX	R44.01 ±R20.66	R20.09 ±R17.18	R10.66 ±R7.60	R23.36 ±R20.35
Theoplus® 200mg TAB	R128.40 ±R51.04	R119.24 ±R50.60	R110.48 ±R40.86	R117.63 ±R47.32
Theoplus® 300mg TAB	R167.57 ±R57.34	R149.59 ±R50.03	R134.52 ±R36.49	R148.56 ±R49.30
UNI-DUR® 400mg TAB	R200.23 ±R10.58	R210.59 ±R63.97	R206.01 ±R0.00	R207.71 ±R52.65
UNI-DUR® 600mg TAB	R304.45 ±R0.00	R319.45 ±R0.00	R279.63 ±R0.01	R303.68 ±R18.60
Uniphyl® 400mg TAB	R154.76 ±R53.69	R136.62 ±R50.74	R127.44 ±R38.67	R138.29 ±R48.78
Uniphyl® 600mg TAB	R192.50 ±R53.76	R176.58 ±R58.50	R154.33 ±R46.77	R172.36 ±R55.02
Alcophyllin® SYR	R36.81 ±R10.76	R18.90 ±R13.85	R8.66 ±R4.74	R20.95 ±R15.39

Table 5.39 Average cost of fluticasone propionate medicine for the study period 2004.

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Seretide® 25/125 INH	R545.72 ±R90.69	R442.80 ±R109.38	R368.77 ±R49.12	R450.14 ±R112.55
Seretide® 25/ 250 INH	R739.85 ±R80.25	R637.56 ±R114.24	R522.63 ±R132.86	R624.28 ±R141.86
Seretide® 25/50 INH	R405.10 ±R29.75	R338.41 ±R93.50	R280.53 ±R45.80	R339.26 ±R81.51
Seretide® 50/100 INH	R402.11	R344.97 ±R66.91	R291.56 ±R51.12	R345.99 ±R75.45
Seretide® 50/250 INH	R541.97 ±R128.96	R443.90 ±R141.02	R404.18 ±R131.00	R458.40 ±R145.32
Seretide® 50/500 INH	R753.90 ±R88.92	R653.61 ±R144.44	R543.13 ±R123.24	R639.77 ±R149.39

Table 5.40 Average cost of Ipratropium/Salbutamol medicine for the study period 2004.

Description	January to April 2004	May to August 2004	September to December 2004	January to December 2004
Combivent® UDV SOL	R151.46 ±R33.17	189.46 ±R187.52	R113.70 ±R26.11	R130.20 ±R34.12
Combivent® MDI INH	R272.06 ±R258.77	R139.48 ±R33.49	R168.13 ±R153.24	R202.47 ±R201.63

Tables 5.36, 5.37, 5.38, 5.39 and 5.40 represent the average cost of products of the five active ingredients with the highest prevalence in table 5.26. In tables 5.36 – 5.40 the difference in cost between the products for the different study periods and for 2004 can be noticed. The influences of new medicine pricing regulations on the individual medicine are also visible from the average cost of the first period to the average cost of the last period.

Although the new SEP could have an effect on the prevalence of these drugs, other major factors that were not part of this study, may *inter alia* include the following:

- Prescriber preferences
- Product advertising
- Patient preferences
- Pharmacist preferences

5.8 CALCULATION OF THE D-VALUE

As discussed in chapter 4, the d-value may be used to calculate the practical significance of differences between prescribed average medicine costs of two compared medicine items.

Steyn (1998:3) recommends the following as guidelines:

[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

With the implementation of the pricing regulations the significance in changes of the average cost per item could be measured. Significant changes can be expected because these new pricing regulations (NPR) may very well have resulted in significant reductions in medicine prices (TAC electronic newsletter, 2005).

5.8.1 MEASURING THE SIGNIFICANCE OF NEW PRICING REGULATIONS WITH THE D-VALUE CALCULATIONS

With the data on the average cost per medicine item, as presented in tables 5.41 and 5.42, the d-values for the bronchodilators and the anti-asthmatics can be determined for the three study periods.

Table 5.41 Average cost per asthma-related medicine item for the three study periods for the bronchodilators

Timeframe	Average cost per bronchodilator medicine item	Standard deviation
January to April	R 213.94 (N =29 337)	± R250.34
May to August	R 172.15 (N = 40 641)	± R308.76
September to December	R 146.78 (N = 40 672)	± R150.13
Weighted average:	**R173.91 (N =44 201)**	**± R 34.21**

Bronchodilators.

January to April, May to August:

$$d = \frac{R213.94 - R172.15}{R308.76}$$

$$d = 0.14$$

May to August, September to December:

$$d = \frac{R172.15 - R146.78}{R308.76}$$

$$d = 0.08$$

January to April, September to December:

$$d = \frac{R213.94 - R146.78}{R250.34}$$

$$d = 0.26$$

It is clear from these calculations that the d-values are low, meaning that the changes in price have a small effect and are non-significant. This result may be due to the relatively high standard deviations. Although the bronchodilators have shown a reduction in average price, the price differences are relatively large with the result that a "large" standard deviation is documented. We could now argue whether the NPR (new pricing regulations) had any real effect on medicine prices.

Table 5.42 Average cost per asthma-related medicine item for the three study periods for the anti-asthmatics

Timeframe	Average cost per anti-asthmatics medicine item	Standard deviation
January to April	R 267.85 (N = 11 002)	(± R 143.34)
May to August	R 240.00 (N = 15 179)	(± R 118.70)
September to December	R 207.26 (N = 18 020)	(± R 93.79)
Weighted average:	**R 233.58 (N = 110 650)**	**(± R 30.74)**

Anti-asthmatics:

January to April, May to August:

$$d = \frac{R267.85 - R240.00}{R143.34}$$

$$d = 0.19$$

May to August, September to December:

$$d = \frac{R240.00 - R207.26}{R118.70}$$

$$d = 0.28$$

January to April, September to December:

$$d = \frac{R267.85 - R207.26.}{R143.34}$$

$$d = 0.42$$

As with the bronchodilators the d-values calculated for the anti-asthmatics have no practical significance, although the d-value for the whole year (January to December) has a more observable effect. A d-value of almost 0.5 shows that the SEP effect on medicine prices is observable and may be practically significant.

Thus, it could be argued that the new pricing regulations had an effect on the anti-asthmatics, but not the same desirable effect on the bronchodilators. Although both medication groups had a price reduction on their average cost per item from January to December, the variation of the prices (causing the standard deviation) plays a major part in the significance and practical importance of the reduction.

5.9 COMBINATION ANTI-ASTHMIC MEDICINE THERAPY

Studies done by Anderson *et al.* (2001: 505) adding formoterol to corticosteroids and Lyseng-Williamson *et al.* (2003: 952) studying the effectiveness of salmeterol/fluticasone propionate in patients with persistent asthma symptoms, have all shown the benefit of combination therapy and its effectiveness in the treatment of asthma.

In this study done, asthma patients used more than one asthma medicine product for the treatment of their condition. As discussed in chapter 2 the severity of the asthma determines the treatment regimen. Mild persistent and mild permitting asthma could both be treated with single combination therapy. Moderate persistent asthma, severe persistent asthma and acute severe asthmatic episode (status asthmaticus) need a multi-combination therapy to treat the condition (Department of Health, 2003:196).

In table 5.43 the frequencies of the different combination therapies are given for the treatment of asthma. From table 5.43 it can be deduced that single combination

medicine therapy represents 53.65% (N = 154 851) of all asthma-related medicine claimed during the study period. The frequencies illustrated in table 5.43 are the number of times that combination therapy was prescribed.

Table 5.43 Prevalence of combination therapy for asthma for the study period January to December 2004

Combinations	January to April	May to August	September to December	Total
One item	23 579	30 225	29 266	83 070
Two items	6 971	9 692	10 772	32 634
Three items	1 269	1 708	2 222	5 199
Four items	172	317	411	900
Five items	25	21	19	65
Six items	3	27	44	74
Seven items	0	0	0	0
Eight items	0	6	5	11

Table 5.44 Prevalence of combination therapy for each of the three study periods 2004

Combinations	Asthma medicine items	Single item therapy (%)	Combination item therapy (%)
January to April 2004	40 339	58.45 (N=23 579)	41.55 (N=16 760)
May to August 2004	55 820	54.15 (N=30 225)	45.85 (N=25 595)
September to December 2004	58 692	49.86 (N=29 266)	50.14 (N=29 426)
January to December 2004	154 851	53.65 (N=83 070)	46.35 (N=71 781)

Table 5.44 illustrates the prevalence of combination therapy for the three study periods and for the total study period 2004. Combination therapy showed an increase in

prevalence towards the end of the study period. Single item therapy represented 53.65% of all asthma medication for the year 2004, representing 58.45% of asthma items during the first period and then decreasing to the last period. Combination item therapy represented 46.35% of all asthma medicine on the database, representing more than half of all asthma medicine in the final study period September to December 2004.(Refer to table 5.44)

The multi-combination therapy is more often prescribed for patients with severe asthma. The standard treatment guidelines and essential drug list (Department of Health, 2003:196) prescribe salbutamol and an inhaled corticosteroid for severe persistent asthma. The rationality behind some of the combinations prescribed could be questioned. Factors that should be taken into account are the following:

- Overdosing
- Increased side-effects
- Drug interactions
- Therapy cost

In the case of $beta_2$ agonist overdosing tachycardia, skeletal muscle tremor, hypocalcaemia, and prolongation of QTc interval are side-effects (Undem *et al.,* 2001: 737). Nevertheless, patients with diabetes, existing heart diseases, high blood pressure, hyperthyroidism and enlarged prostate, or a history of seizures should take these drugs with caution (Simon *et al.,* 2000). With an increase in dosage there is an increase of side-effects. The side-effects of the different drugs are discussed in chapter 2.

Strong evidence consistently indicates that long-acting inhaled $beta_2$-agonists added to low-medium-dose inhaled corticosteroids, improved outcomes. Adding a leukotriene modifier or theophylline to inhaled corticosteroids or doubling the dose of inhaled corticosteroids also improved outcomes, but the evidence is not as substantial. An increased number of studies evaluating combination therapy primarily can be observed, very likely as a result of the development of fixed-doses combinations of the long-acting inhaled $beta_2$-agonists and inhaled corticosteroids (salmeterol plus fluticasone propionates, now FDA-approved, and formoterol plus budesonide, under development). The ongoing preference to minimise the dose of corticosteroids, especially for patients taking high doses, and to reduce the possibility of adverse side effects, has stimulated studies of adjunctive therapies (Peterson, 2002).

Table 5.45 Asthma medicine item combinations prescribed during 2004.

Items	Combinations	Prevalence	Average cost of total combination (R)	Combinations	Prevalence	Average cost of total combination (R)
2	Berotec® 100 15ml INH Budeflam® 100/300 GEN	10	291.11 (±R37.75)	Astavent® M.D. 200INH Beclate® 100mcg INH	45	149.76 (±R2617)
3	Berotec® 100 15ml INH Budeflam® 100/300 GEN Oxis® Turbuhaler 9	2	224.22 (±R0.00)	Asthavent® M.D 200INH Beclate® 100mcg INH Atrovent® MDI	2	310.57 (±R21.96)
4	Berotec® 100 15ml INH Berotec® INH 0.1% SOL Budeflam® 100/300 GEN Theoplus® 300mg TAB	2	716.67 (±R0.00)	Asthavent® M.D 200INH Asthavent® M.D 200INH Atrovent® Beta UDV Atrovent® Beta UDV	1	90.16 (±R0.00)
5	Berotec® 100 15ml INH Berotec® 100 15ml REF Uniphyl® 400mg TAB Venteze® Complete INH Venteze® Inh REF	1	671.47 (±R0.00)	Asthavent® M.D. 200INH Atrovent® 0.25mg UDV Berotec® 0.5 UDV SOL Inflammide® 100 MAC Pulmicort® 0.5mg UDV	1	613.16 (±R0.00)
6	Berotec® 100 15ml INH Berotec® 100 15ml REF Pulmicort® TURBO 200 Uniphyl® 400mg TAB Venteze® INH REF Venteze® Complete INH	1	1366.36 (±R0.00)	Asthavent® M.D. 200INH Asthavent® M.D. 200INH Beclate® 200mcg INH Beclate® 200mcg INH Serevent® 120 INH Serevent®120INH300dose	1	857.38 (±R0.00)

Table 5.45 represents examples of combination therapy prescribed during 2004. The two-item combination therapy is the standard treatment according to the Department of Health (2003:196). Every item added to this treatment increases the cost, possible side-effects and possible drug interactions. Only when a patient does not respond to this standard treatment should additional medicine be added

Besides the side-effects of drugs, a non-physical factor affecting patients, forms part of the cost of the therapy. With an increase in products used in a combination there is a definite increase in the cost of the total therapy. (Refer to table 5.45)

It is clear that multi-combination therapy is more expensive than single- combination therapy. Although in this study the outcomes of the treatment are not available, it is clear that in some asthma patients, the severity of the asthma needs a multi-combination dosage to treat the condition or keep it under control. In America severe asthma sufferers spend $12,813 a year caring for their asthma. A 5% shift from severe to moderate asthma would save approximately $1.4 billion annually in total costs, researchers concluded in a study in the June 2003, Journal of Allergy and Clinical Immunology (Cisternas *et al.,* 2003: 1212). To justify the treatment cost, the treatment itself must be justified and rational. And as already discussed, the severity of the condition has its own standard treatment.

5.9.1 COMBINED ACTIVE INGREDIENT THERAPY

In some asthma medicine items active ingredients were combined to form a combination medicine item. These medicine items are illustrated in table 5.46.

Table 5.46 Combined combinations therapy

Active ingredient combinations	Number of items	Prevalence of asthma medicine (%)
Ipratropium/Salbutamol	9 575	6.18
Fenoterol/Ipratropium	8 206	5.30
Theophyllin/Etophyllin	2 643	1.71
Budesonide/Formoterol	2 454	1.58
Aminophylline/Ephedrine	413	0.27
Etafedrine/Ambuphullin	309	0.20
Theophyllin/Ephedrine	13	0.00
Total	**23 613**	**15.25**

Asthma treatment in such a combined form is prescribed to improve patient compliance by using only one medicine item. These medicine items represent 15.25% of asthma medicine for the study period 2004.

5.10 THE EFFECT OF THE SINGLE EXIT PRICE REGULATION ON ASTHMA-RELATED MEDICATION.

As discussed in chapter 3.9 the new medicine pricing regulations had an influential effect on the cost of medication as a whole. Medicine prices decreasing meant that patients could change from generic medicine to the innovator product. The profit margins for pharmacists were regulated as by the new legislation (TAC electronic newsletter, 2005).

On 2 May 2004, some of the provisions of the new medicine pricing legislation came into effect and the single exit price (SEP) came into effect on 2 June 2004. Pharmacists were no longer able to price medicines in the same way as before from 27 August 2004 (TAC electronic newsletter, 2005).

Table 5.48 Average cost per asthma-related medicine item during the study period.

Timeframe (period)	Average cost per medicine item (bronchodilators)	Average cost per medicine item (anti-asthmatics)	Average cost per medicine item (Total database)
January to April	R213.94 (± R250.34) (N = 29 337)	R 267.85 (± R 143.34) (N = 11 002)	R 145.89 (± R 283.72) (N = 1 363 585)
May to August	R 172.15 (± R308.76) (N = 40 641)	R 240.00 (± R 118.70) (N = 15 179)	R 124.23 (±R 208.03) (N = 1 953 845)
September to December	R 146.78 (± R150.13) (N = 40 672)	R 207.26 (± R 93.79) (N = 18 020)	R 110.42 (± R 202.84) (N = 1 988 452)
Average:	**R173.91** **(± R 34.21)**	**R 233.58** **(± R 30.74)**	***R 126.85*** **(± R 17.88)**

*All medicine items on the database

Table 5.48 clearly indicates the decrease in the average price per medicine item for both groups of asthma-related medication. The price showed a decrease of 19.53% with the implementation of the single exit price for the bronchodilators and 10.40% for anti-asthmatics (d-values discussed in section 5.9). A further decrease resulting from the SEP regulations, could be detected in the price of the bronchodilators and the anti-asthmatics, respectively 14.74% and 13.64%, indicating the price reducing effect of the legislation on medicine cost. This gave a total cost reduction of 31.39% and 22.62% for the bronchodilators and anti-asthmatic medications respectively.

A cost reduction of 24.31% (all items included) occurred on the total database. Thus it is clear that the bronchodilators in comparison with the other medication became relatively cheaper with a largerr reduction in price. These observable decreases in price of the bronchodilators, larger than those of anti asthmatics, could cause the prevalence to shift more towards the bronchodilators. The other problem this could lead to is that pharmacists must sell more medication to retain the same profits. This may cause a problem due to the fact of prescriptions dispensed and time per patient for patient care. This aspect was not further investigated in this study.

5.11 Chapter summary

In this chapter the results of the empirical study were discussed. The prevalence and cost of asthma medicine were established. The effect of the new pricing regulations on the cost of asthma medication was also analysed.

Hereby the first, eigth, ninth and tenth research qeustions have been answered and their research objective reached.

CHAPTER 6
CONCLUSIONS AND RECOMMENDATIONS AND LIMITATIONS

6.1 Introduction

Conclusions and recommendations regarding the management of asthma will be made in this chapter. Limitations regarding this study will be stated and recommendations for future research will be made.

6.2 Conclusions

The following conclusions can be formulated regarding the first four (theoretical or literature) objectives of the research:

- The **first research objective** was to investigate the prevalence of asthma in the general public. The investigation was conducted by means of information on a database in a South African setting. It was concluded that asthma conditions are frequent and are among the most common entities encountered in the medical practice (Prakesh *et al.*, 2003) (Refer to section 3.1). Asthma is diagnosed on the basis of certain signs and symptoms, which can be substantiated with a clinical investigation (Refer to section 2.4.). In this study asthma medicine represented 4.46% (N = 115 684) of medicine prescribed on the medicine claims database (N = 2 595 254) and 18.40% of all respiratory system medicine (N=628 754) during 2004 (Refer to table 5.1).

- The **second research objective** was to conceptualise what asthma together with its management entails. Managed care is a belief that a health care system should be in place to monitor health care activities for the better of everybody concerned.Managed care should endeavour to keep people healthy; and, when they are suffering from an illness or injury, should endeavour to assure the right treatment in the right setting by the right person. In the management of asthma, clinical decision making is primarily directed toward achieving the best outcome for the

patient (Stempel *et al.,* 2002: S504). It is important that the type of asthma the patient has is defined, because treatments and management of asthma will differ depending on the severity of the patients' asthma (American Academy of Allergy Asthma and Immunology, 2002).

The achievements of asthma control are related to improvements in health related quality of life (Lyseng-Williamson *et al.,* 2003: 956). Asthmatic patients may benefit from the introduction of self-management plans that provide an individually tailored care plan to cope with variations in their asthma severity (Boyter *et al.,* 2000:553).

The goals of long-term management of asthma should include the following (Buist, 2002):

- Achievement and maintenance of control of symptoms
- Prevention of asthma exacerbations
- Maintenance of pulmonary function as close to normal levels as possible
- Maintenance of normal activity levels, including exercise
- Avoidance of adverse effects from asthma medications
- Prevention of the development of irreversible airflow limitation
- Prevention of asthma mortality

- The **third research objective** was to determine which pharmaceutical care principles should be followed in the management of asthma. As explained in chapter 2 (section 2.2), the pharmaceutical care process consists of three processes, *i.e.*
    - assessment
    - care planning
    - follow-up evaluation

  In chapter 2 (section 2.4) the diagnoses of asthma in children and in adults were discussed. Clinical tests done to test for asthma in patients were listed in table 2.3. The severity of asthma must also be determined with the diagnosis for the correct treatment to be implemented. For the care plan of asthma, it is important that patients are counselled on the trigger factors of asthma. The preventative medication for asthma was listed in table 2.7. The patients must also be counselled on the correct use of inhaler devices. Routine care would include clinical assessment of airway function over time. Spirometry is recommended at the initial assessment and at least every year or second year after treatment has been initiated and the symptoms and peak expiratory flow have stabilised.

- The **fourth research objective** was to determine the spectrum of anti-asthma agents. Asthma medicine includes the following:
    - Corticosteroids – Beclomethesone, Budesonide, Fluticasone
    - Short acting B_2 agonists – Salbutamol, Terbutaline, Fenoterol
    - Long acting B_2 agonists – Formoterol, Salmeterol xinofoate
    - Mast cell stabilizers – Sodium cromoglycate, Nedocromil
    - Anticholinergics – Ipratropium bromide, tiotropium
    - Leukotriene receptors antagonists – Montelukast, Zafirlukast
    - Xanthines – aminophyllin, Oxtrphyllin, Theophyllin

Tables 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16 show the different asthma medications and their dosages.

- The **fifth research objective** was to conceptualise what pharmaco-economic implications entail. Economics is about trade offs and choices between wants, needs, and scarcity of resources to fulfil these wants. Pharmaco-economic research identifies, measures and compares the costs (*i.e.* resources consumed) and consequences (clinical, economic and humanistic) of pharmaceutical products and services. The ultimate aim of pharmaco-economics is to assist the decision makers in achieving allocation efficiency in the health care system. This is in response to the increased need for accountability during the age of cost-containment in health care. The objective of pharmaco-economic evaluation is to provide evidence-based information that may be used in reimbursement decisions. Pharmaco-economic analysis can be performed on all pharmaceutical products for which an application for reimbursement is submitted. Cost-effectiveness analysis can be used when the treatment programmes to be compared give the same type of health outcome, e.g. two drugs that reduce the number of asthma attacks. In such a case the health outcomes can be compared. Cost of illness studies provide insight into the economic impact of a disease. Some countries attempt to separate economic burden into disease-attributable direct and indirect costs. It was determined that in this study (according to a database in a section of the South African health care system) the financial burden on asthma patients amounted to R 29 567 363.00.

- The **sixth research objective** was to conceptualise what pharmaco-epidemiology entails. Pharmaco-epidemiology can be defined as the study of the use and the effects of drugs in large groups of people (Andrade *et al.*, 2000: 5). It can be viewed as an epidemiological discipline with particular focus on drugs. Pharmaco-epidemiological methods are increasingly being used to evaluate the total costs associated with drug therapy (Andrade *et al.*, 2000: 4). These studies included evaluations of the total effect of dugs on utilisation of medical services and costs of total medical care. In this study the total cost of asthma treatment was not investigated. Only the cost of asthma medicine was investigated. The prevalence of asthma medicine in the study population did not increase significantly. (Refer to table 5.2, 5.6 and 5.7).

- The **seventh research objective** was to determine through the literature study what costs the medical treatment of asthma would incur. In a good pharmaco-economic evaluation, all relevant costs are included. Costs are broadly classified as direct, indirect and intangible costs. Direct costs include the cost of goods and services that can be purchased in the marketplace. Researchers found a significant difference in direct and indirect costs between mild and severe asthma sufferers. Total costs for mild asthma sufferers averaged $2,646 per person, each year, while severe asthma sufferers averaged $12,813 (Cisternas *et al.*, 2003). The average spent for all asthma sufferers was $4,912. In this study a South African database was selected and the total cost of asthma was R 29 567 363.00. From the database no distinction could be made with regard to asthma severity. The final group of costs, and the most difficult to measure, are the intangible or 'psychosocial' effects of illness. Pain, suffering or other restrictive aspects affecting quality of life are intangible and, by definition, difficult to quantify. In this study the differences between the direct, indirect, and intangible costs of asthma were also discussed (refer to section 3.6, p76). For this study the direct medicine costs of asthma were investigated.

- The **eighth research objective** was to determine what the relevance and frequency of generic substitution of the different categories of anti-asthma agents would be. A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, and route of administration, quality, performance characteristics and intended use. Many products that do not use chlorofluorocarbons (CFC) are already

available for the treatment of asthma and chronic obstructive pulmonary disease. These products are not necessarily "official" direct alternatives to CFC Metered Dose Inhalers but may in many patients serve as a useful medication that could replace the need for a particular CFC Metered Dose Inhaler. In comparison with the total database (33.49%, N = 5 305 882), the generic substitution of asthma medication is far less, representing 24.18% of medication prescribed for asthma. From tables 5.17 and 5.18 (refer to section 5.7) it can be deduced that although the cost of generic medicine is less than that of the innovater medicine, the prevalence of the innovater medicine is far greater than that of the generic medicine.

- The **ninth research objective** was to determine the usage and cost of the different anti-asthmatic agents. Tables 5.27, 5.28, 5.29, 5.30, 5.31, 5.32, 5.33, 5.34 and 5.35 indicate the prevalence percentages of anti-asthmic active ingredients for 2004. To compare the averages of these drugs more efficiently, a d-value was calculated. With the data on average cost per medicine item, as presented in tables 5.6, 5.7, 5.8, 5.9, 5.38 and 5.39 the d-values for the bronchodilators and the anti-asthmatics could be determined for the three study periods. It is clear from these calculations (refer to section 5.8) that the d-values for both the anti-asthmatics and the bronchodilators are low, meaning that the changes in price have a small effect and are non-significant.

- The **tenth research objective** was to investigate the influence of new medicine pricing systems on the cost of anti-asthmatic agents. In this study, pertaining to a South African setting, it could be accepted that during January to April 2004 there were no "legislation restrictions" on prices, therefore the "traditional tariffs" were claimed. The study period from May to August took into account the introduction of the SEP, that restricted pharmaceutical companies to supply the medication at a "single exit price". Thus the data for this term reflected the in-phasing of the regulations on medicine prices. September to December reflected the full implementation of the SEP and therefore also the impact it exercised on medicine items. The data (refer to table 5.45) clearly indicated the decrease in average price per item for both groups of asthma-related medication. The price showed a decrease of 19.53% with the implementation of the single exit price for the bronchodilators and 10.40% for anti-asthmatics. A further decrease from the SEP price of the

bronchodilators and the anti-asthmatics, respectively 14.74% and 13.64%, indicated the price reducing effect of the legislation on medicine cost.

- The **eleventh research objective** was to compare the prevalence of asthma medication during 1995 with 2004. The cost prevalence for each year was calculated for each study year. A slight decrease in the CPI from 1995 to 2004 indicated that the therapy utilised for treatment of asthma was relatively less expensive in 2004 than in 1994/5 in comparison with the total database. This study revealed that the average cost per prescription for asthma treatment did not increaseto a greater extent than the average cost of the medicine claimed on the total database. A comparison was also made between generic substitution (refer to table 5.19) and asthma medicine utilsed. The prevalence of medicine groups was also compared (Refer to table 5.20) .

- The **final research objective** was to investigate the rationality of combination therapy prescribed for the treatment of asthma. The standard treatment guidelines and essential drug list (Department of Health, 2003:196) prescribe salbutamol and an inhaled corticosteroid for severe persistent asthma. With an increase in dosage there is an increase of side-effects. The side-effects of the different drugs were discussed in chapter 2. Besides the side-effects of drugs, attention was paid to a non-physical factor affecting patients, namely the cost of the therapy. With an increase in products used in a combination there would be a definite increase in the cost of the total therapy. The prevalence of combination therapy in asthma was illustrated in table 5.44. Single medicine therapy had a much higher prevalence than combination therapy and represented 53.65% of the asthma medicine prescribed. Combination therapy had an increase in prevalence throughout the three study periods and constituted more than half of the medicine utilised in the third study period.

6.3 Limitations and shortcomings of the research

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

- After data refinement all data entered on the database were considered to be accurate and correct.
- Costs indicated on the database were considered correct.

- The database did not contain information on the diagnosis of patients or the patients' history.
- The cost-prevalence index is only limited to cost and does not provide information on the patients' clinical outcomes.

6.4 Recommendations

According to the results of this study the following recommendations can be made, *i.e.* recommendations with regard to the management of asthma in asthma patients:

- The prevalence of asthma should be monitored continuously as well as the usage patterns of asthma medicine. This would enable further studies to investigate changes in prevalence and cost of asthma medicine, prevalence of generic substitution and the effectiveness of asthma management.

- The outcomes of medicine treatment should be researched to investigate
    - patient co-operation with the drug treatment;
    - effectiveness of certain combinations; and
    - duration of asthma treatment to reach positive outcomes.

- Average cost of asthma (per prescription and per item) is higher than that of the database (refer to table 5.2). It is therefore recommended that the generic substitute or equivalent be prescribed as frequently as possible.

The following recommendations for further research can be made on the basis of the results of this study:

- Studies should be conducted on the influence of occupational and environmental factors on the prevalence and the medicine treatment costs of asthma.

- The influence of demographics on the prevalence of asthma should be researched as well as the choice of medicine treatment.

- A further comparison study on the cost of asthma should be launched in future to evaluate the long-term effects of the new pricing legislation.

- The influence of the single exit price on the pharmacist and on the prevalence of the product should be investigated.

6.5 CHAPTER SUMMARY

In this chapter the conclusions, limitations and recommendations were discussed.

CHAPTER 7
BIBLIOGRAPHY

ALLENSWORTH, C., BUNTGEN, R., COTO, J.A., GOULD, K., KALKOWSKI, T., NAUJOKAITIS, J. & WADUM, M. 2001. A report on the growing problem of asthma. 48p.

AL-SHAQHA, W.M.S. & ZAIRI, M. 2001. Pharmaceutical care management: a modern approach to providing seamless and integrated health care. *International journal of health care quality assurance*, 14: 282-301.

AMERICAN ACADEMY OF ALLERGY OF ALLERGY AND IMMUNOLOGY. 2002. Tips to remember: asthma triggers and management. [Web:] http://www.aaaai.org/patients/publicedmat/tips/asthmatriggersandmgmt.stm. [Date of access: 4 May 2004].

AMERICAN ACADEMY OF ALLERGY OF ALLERGY AND IMMUNOLOGY. 2003. Tips to remember: asthma and pregnancy. [Web:] http://www.aaai.org/patients/publicedmat/tips/asthmaandpregnancy.stm. [Date of access: 30 Aug. 2004].

AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY. 1997. Guidelines for the diagnosis and management of asthma. [Web:] http://www.acaai.org/Member/Practice_Resources/guidelines.htm. [Date of access: 27 May 2004].

AMERICAN LUNG ASSOCIATION. 2002. Asthma: an impact assessment. [Web:] http://www.texaslung.org/educationalresources/diseases/asthmaimpactassessment.htm. [Date of access: 27 Jan. 2004].

AMERICAN SOCIETY OF CONSULTANT PHARMACISTS. 1998. Statement on Pharmaceutical care. [Web:] http://www.ascp.com/public/pr/policy/pharmaceutical.shtml. [Date of access: 1 Feb. 2004].

ANDERSSON, F., STAHL, E., BARNES, P.J., LOFDAHL, C.G., O'BYRNE, P.M., PAUWELS, R.A., POSTMA, D.S., TATTERSFIELD, A.E. & ULLMAN, A. 2001. Adding formoterol to budesonide in moderate asthma: health economics results from the FACET study. *Respiratory medicine*, 95:505-512.

ANDRADE, S. & GURWITZ, J. 2000. Pharmacoepidemiology and the elderly. [Web:] www.worldscibooks.com/medsci/ etextbook/p085/p085_chap1.pdf. [Date of acces: 27 Jan. 2005].

ARNOLD, J.K. 2005. Common health insurance terminology. [Web:] http://www.floridahealthinsurance.com/glossarydef.htm. [Date of access: 13 Mar. 2005]

ASTHMA AND RESPIRATORY FOUNDATION OF NEW ZEALAND. 2000. Best practice evidence-based guideline: the diagnosis and treatment of adult asthma. [Web:] http://www.asthmanz.co.nz/info_health_profs.php. [Date of access: 31 Jul. 2005].

BARNES, N.C., THWAITES, R.M.A. & PRICE, M.J. 1999. The cost-effectiveness of inhaled fluticasone propionate and budesonide in the treatment of asthma in adults and children. *Respiratory medicine*, 93: 402-407.

BIRNBAUM, H.G., LEONG, S.A., OSTER E.F., KINCHEN K. & SUN, P. 2004. Cost of Stress Urinary Incontinence: a claims data analysis. *Pharmacoeconomics*, 22: 95-105.

BUEHLER, G. 2004. Office of the generic drugs director. [Web:] http://www.fda.gov/cder/ogd/welcome_to_ogd.htm. [Date of access: 20 Feb. 2005].

BMJ. 1997. What is epidemiology? [Web:] http.//www.bmj.bmjjournals.com/epidem/epid.1.html. [Date of access: 19 Apr. 2005].

BOUSHEY, H.A. 2001. Drugs used in asthma. (*In* Katzung, G.B., *ed.* Basic & clinical pharmacology. New York: Mcgraw Hill. p.333-381.)

BOYTER, A., CURRIE, J., DAGG, K., GROUNDLAND, F. & HUDSON, S. 2000. Pharmaceutical care: asthma. *The pharmaceutical journal*, 264: 546-556.

BUIST, A.S. 2002. Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes. *European respiratory journal*, 21: 30S-35S.

BYFORD, S., TORGERSON, D.J. & RAFTERY, J. 2000. Cost of illness studies – education and debate. [Web:] http://www.findarticles.com/p/articles/mi_m0999/is_7245_320/ai_62648661. [Date of access: 1 Jun. 2005].

CAIRNS, C. & EVELEIGH, M. 2000. Involving community pharmacists in asthma care: lessons from a pilot study. The pharmaceutical journal, 265:136-140.

CANADIAN ASTHMA CONSENSUS GUIDELINES, 2003. Treatment algorithms. [Web:] http://www.asthmaguidelines.com/tools.html. [Date of access: 27 Jul. 2005].

CANADIAN LUNG ASSOCIATION, 2003. Living with asthma: asthma diagnosis. [Wed:] http://www.lung.ca/asthma/diagnosis.html [Date of acces: 24 Apr. 2004].

CENTRE OF DISEASE CONTROL AND PREVENTION. 2003. National asthma control program. [Web:] http://www.cdc.gov/nceh/airpollution/asthma/asthmaAAG.htm. [Date of access: 4 Feb. 2004].

CHEN, J.C, & MANNINO, D.M. 1999. Worldwide epidemiology of chronic obstructive pulmonary disease. *Current opinions in pulmonary medicine*, 5: 93-99.

CHESSNUTT, M.S., PRENDERGAST, T.J. & STAUFFER, J.L. 1999. Lung. (*In* Larence, M.J., McPhee, S.J. & Papadakis, M.A. Current medical diagnosis and treatment. 38th ed. London: Appelton & Lang. 1672p.

CHUEN, L.S. 2003. An introduction to pharmacoeconomics evaluation in rheumathology. *Journal of rheumathology*, 6: 192-200.

CIPOLLE. R.J., STRAND, L.M. & MORLEY P.C. 1998. Pharmaceutical care practice. New York : McGraw-Hill. 359p

CISTERNAS, M.G., BLANC, P.D., YEN, I.H., KATZ, P.P., EARNEST, G., EISNER, M.D., SHIBOSKI, S. & YELIN, E.H. 2003. A comprehensive study of the direct and indirect cost of adult asthma. *Journal of allergy and clinical immunology*, 6:1212-1218.

COUNCIL OF MEDICAL SCHEMES. 2002. Annuel report of the registrar of medical Schemes 2002-3. 63p

CURTISS, F.R. .1989. Managed health care. *American journal of health-system pharmacy*, 46: 742-763.

DAMBRO, M.R. 1999. Griffith's 5-minute clinical consult. Philadelphia: Lippincott Williams & Wilkins.1325p.

DE LISSOVOY, G. & SUBEDI, P. 2002. Economic evaluation of enoxaparin as prophylaxis against venous tromboembolisms in serious I11medical patients: A US perspective. *The American journal of managed care*, 8: 1082-1088.

DEPARTMENT OF HEALTH, 1998. Standard treatment guidelines and essential drug list: pediatrics. Pretoria: The national department of health. p 304.

DIMASI, J.A., CAGLARCAN, E., & WOOD-ARMANY, M. 2001. Emerging role of pharmacoeconomics in the research and development decision-making process. *Pharmacoeconomics*, 19: 753-766.

EUCOMED. 2005. The best way of allocating resources. [Web:] http://www.eucomed.be/?x=4&y=24&z=82. [Date of access: 21 Jan. 2005]

EMERGIS, 2003. Drug utilization review. [Web:] http://www.emergis.com/en/solutions/pdf/Healthassure.pdf. [Date of access: 6 Aug. 2005].

EVERARD, M.L. 2003. Role of inhaler competence and contrivance in "difficult asthma". *Pediatric respiratory reviews*, 4(2):135-142.

FDA/CENTER FOR DRUG EVALUATION AND RESEARCH. 2005. Office of generic drugs: What is generic drugs? [Web:] http://www.fda.gov/cder/ogd/. [Date of access: 5 Jun. 2005].

FLEURENCE, R. 2003. An introduction to health economics. *The pharmaceutical journal*, 270: 679-681.

GIBBON. C.J., ed. 2003. South African medicines formulary. Pinelands: South Afrcan medical association. 569p.

GRADY, D. 2005. Experts to consider withdrawal of asthma drugs. [Web:] http://www.nytimes.com/2005/07/13/health/13asthma.html?incamp=article_popular_1. [Date of access: 27 Aug. 2005].

HALLAS, J. 2001. Pharmacoepidemiology- current opportunities and challenges. *Norwegian journal of epidemiology*, 11: 7-12.

HEALTH ASSURE, 2003. Health assure: drug utilization review. [Web:] http://www.emergis.com/en/solutions/pdf/Healthassure.pdf. [Date of access: 24 Jun. 2005].

HEALTH & SAFETY EXECUTIVE. 2003. Draft approved code of practice on occupational asthma: regulatory impact assessment (post consultation). [Web:] http://www.hse.gov.uk/ria/chemical/asthma.htm. [Date of access: 29 Apr. 2005].

HEALTH GOODS. 2005. The growing problem of asthma in children. [Web:] http://www.healthgoods.com/Education/Health_Information/Asthma_and_Allergies/children_asthma.htm. [Date of access: 27 Feb. 2005].

HENNESSY, S., BILKER, W.B., ZHOU, L., WEBER, A.L., BRESSINGER, C., WANG, Y. & STORM, B.L. 2003. Retrospective drug utilization review: prescribing errors and clinical outcomes. *Journal of American medical association*, 290: 1494-1499.

INTEGRATED HEALTHCARE ASSOCIATION, 2005. [Web:] http://health-care-depot.com/evolutionhealthcaresystem/. [Date of access: 6 Aug. 2004].

JEENA, P., LUYT, D. & MORRIS, A. 2004. What is asthma? [Web:] http://www.capegateway.gov.za/eng/pubs/public_info/W/67819. [Date of access: 5 Apr. 2005].

JONES, P. 2005. Management of asthma: beyond the cost. [Web:] http://www.worldallergy.org/educational_programs/world_allergy_forum/denver2003/jones.shtml. [Date of access: 20 Apr. 2005].

LACROIX, A., JACQUEMET, St., & ASSAL, J.P. 1995. Patients experiences with their disease: learning from the differences and sharing the common problems. *Patient education and counseling*, 26:301-312

LINDGREN, B., SEARS, M.R., CAMPBELL, M., VILLASANTE, C., HUANG, S., LINDH, A., PETERMANN, W., SVENSSO, K., BERGGREN, F. & PAUWELS, R.A. 2005. Cost-effectiveness of formoterol and salbutamol as asthma reliever medication in Sweden and in Spain. International journal of clinical practice, 59: 1-62.

LYSENG-WILLIAMSON, K.A. & PLOSKER, G.L. 2003. Inhaled salmetarol/fluticasone propionate combination. *Pharmacoeconomics*, 21:951-989.

MAKOID, M.C. 1999. Pharmaceutical calculations. [Web:] http://pharmacy.creighton.edu/pha313/book/R-Introduction.pdf. [Date of access: 18 Mar. 2004].

MASSACHUSETTS DIVISION OF MEDICAL ASSISTANCE, 2004. Drug utilization review program. [Web:] http://www.umassmed.edu/dur/ [Date of access: 2 Apr. 2005]

MCDONALD, C.F. & BURDON, J.G.W. 1996. Asthma in pregnancy and lactation. *The medical journal of Australia*, 165: 485-488.

MOORE, T., BYKOV, A., SAVELLI, T. & ZAGORSKI, A. 1997. Guidelines for implementing drug utilization review programs in hospitals. Moscow: Russia pharmaceutical management project. 45p.

NAGAPPA, A. N., KOLE, P. L. & GIRISH, K. 2002. Pharmacoeconomics and its relevanceto therapeutics and industrial practice. [Web:] http://pharmabiz.com/article/detnews.asp?articleid=12185§ionid=46. [Date of access: 7 Jan. 2005].

NATIONAL ASTHMA CAMPAIGN. 2002. Asthma Audit 2002:Children with asthma. [Web:] http://www.asthma.org.uk/about/factsheet38.php. [Date of access: 2 Apr. 2005].

NATIONAL ASTHMA CAMPAIGN. 2005. Significance of asthma to the community. [Web:] http://www.nationalasthma.org.au/publications/costs/findings.html. [Date of access: 27 Apr. 2005].

NATIONAL ASTHMA COUNCIL OF AUSTRALIA. 2004. Assessing asthma severity. [Web:] http://nationalasthma.org.au/papers/ltras/assessing_severity.htm. [Date of access: 6 April 2004].

NATIONAL ASTHMA EDUCATION AND PREVENTION, NATIONAL INSTITUTES OF HEALTH. 1997. Practical guide for the diagnosis and management of asthma. 52p.

NATIONAL COMMITTEE FOR QUALITY ASSURANCE, 2005. Asthma disease management. [Web:] http://www.qualityprofiles.org/quality_profiles/case_studies. [Date of access: 8 January 2005].

NATIONAL DEPARTMENT OF HEALTH, 2003. The Standard treatment guidelines and essential drug list. Pretoria : National Department of Health. 365p.

NATIONAL GUIDELINE CLEARINGHOUSE, 2003. The diagnosis and treatment of adult asthma. [Web:] http://www.guideline.gov/summary/summary.aspx?. [Date of access: 12 Jul. 2004].

NATIONAL HEART, LUNG AND BLOOD INSTITUTE, 2002. Disease and conditions index. {Web:] http://dci.nhlbi.nih.gov/Disease/Asthma/Asthma_treatment.html. [Date of access: 30 Jan. 2005]

NATIONAL PRESCRIBING CENTRE. 2000. An introduction to health economics (part 2): Applying health economics. MeReC Briefing, 14: 1-8.

NORWEGIAN MEDICINES AGENCY. 2004. Norwegian guidelines for pharmacoeconomic analysis in connection with applications for reimbursement. [Web:] http://www.legemiddelverket.no/eng/reg/pharmacoeconomic-analysis-guidelines.htm [Date of access: 27 May 2005].

OMZINKOWSKI, R.J., WANG, S., MARDER, W.D., AZZOLINI, L. & SCHUTT, D. 2000. Cost implications for the use of inhaled antiinflammory medications in the treatment of asthma. *Pharmacoeconomics*, 18: 253-264.

ORLEWSKA, E. & MIERZEJEWSKI, P. 2001. Polish guidelines for conducting pharmacoeconomic evaluations. [Web:] http://www.farmaokoekonomika.pl/wytyczne_ang.pdf. [Date of access: 28 Feb. 2005].

PAM POHLY'S NET GUIDE, 2005. A glossary of terms in managed care. [Web:] http://www.pohly.com/terms_c.html [Date of access: 27May 2005].

PERSSON, U. & GHATNEKAR, O. 2003. Cost-effectiveness analysis of inhaled corticosteroids in asthma: a review of the analytical standards. *Respiratory medicine*, 97: 1-11.

PHARMACY AUDIT. 2000. Pharmaceutical care audit: Ready to go series. [Web:] http://www.managingmedicines.com/Pharmaceutical_Care_Audit_Pruce.pdf. [Date of access: 5 Aug. 2004].

PHARMAPATH'S GLOSSARY OF DRUG BENEFITS TERMS, 2003. Pharmapath's glossary of drug benefits terms. [Web:] http://www.pharmapath.com/PP/PP_glossary.html. [Date of access: 6 May 2005].

PRINCIPLE FINANCIAL GROUP, 2001. Drug utilization review: concurrent DUR. [Web:] http://www.principal.com/grouplh/selffunded/utilize.htm. [Date of access: 6 May 2005].

QUEENSLAND HEALTH, 2001. The health outcomes plan for asthma: 2001- 2006. [Web:] http://www.health.qld.gov.au/hop/asthma_background.PDF. [Date of access: 28 Apr. 2005].

QUINN, C. 2004. The cost effectiveness of levalbuterol versus racemic albuterol. The *American journal of managed care*, 10: s153-s157.

RATIONAL THERAPY. 2004. Evaluating cost-effectiveness and outcomes of asthma treatment. [Web:] http://www.aon.com/about/publications/pdf/med_monographs/astma_treatments.pdf [Date of access: 5 March 2005].

ROUSSELL, H.M. 1998. Building a practice in pharmaceutical care. *The pharmaceutical journal*, 260:874-876.

SALKELD, G., MORRELL, S., WEBSTER, F., TAYLOR, R. & KERR C. 1996. Economic cost of health. [Web:] http://www.nohsc.gov.au/OHSInformation/NOHSCPublications/misc/kerr/1_vol2.htm. [Date of access: 1 Jun. 2005].

SCHIMMER, B.P. & PARKER, K.L. 2001. Drugs used in the treatment of asthma (*In* Hardman, J.G. & Limbird, L.E., *ed.* The pharmacological basis of therapeutics. New York: Mcgraw-Hill. p. 1649-1677.)

SCULPHER, M. J. & PRICE, M. 2003. Measuring the cost and consequences in economic evaluation in asthma. *Respiratory medicine,* 97: 508-520.

SERFONTEIN, C.B. 1996. Drug utilization review: A third party payers perspective. Potchefstroom: PU vir CHO, (Dissertation-M.Pharm.) 217p.

SHALALA, D.A. 2000. Asthma: epidemic of a chronic disease. [Web:] http://aspe.hhs.gov/sp/asthma/overview.htm. [Date of access: 5 Oct. 2004].

SIMON, H., ETKIN, M.J., GODINE, J.E., HELLER, D. SHELLITO, P.C. & STERNS, T.A. 2000. Asthma in adults. [Web:] http://wellness.ucdavis.edu/medical_conditions_az/asthmainadults04.html [Date of access: 5 Mar. 2004].

SINGH, V., SINHA, H.V. & GUPTA, R. 2002. Barriers in the management of asthma and attitudes towards complementary medicine. [Web:] www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12412985&dopt=Abstract. [Date of access: 27 Jun. 2004].

SOUTH DAKOTA DEPARTMENT OF SOCIAL SERVICES, 2004. South Dakota Medical Assistance Program. [Web:] https://www.state.sd.us/social/Medical/provider/Pharmacy/Pharmacy%20Manual.pdf. [Date of access: 7 Apr. 2005].

STEMPEL, D.A., STANFORD, R.H., TWAITES, R.M.A. & PRICE, M.J. 2000. Cost-effecacy comparison of inhaled Fluticasone propionate and Budesonide in the treatment of asthma. *Clinical therapeutics*, 22: 1562-1574.

STEMPEL, D.A. & KELLY, H.W. 2002. Approaching value in asthma management: The need to integrate clinical and economic research with the basic science. *Journal of allergy and clinical* immunology. 109: S503-S510.

STORMS, W.W. 2003. Unmet needs in the treatment of allergic asthma: Potential role of novel biologic therapies. *Journal of managed care pharmacy*, 9: 534-543.

SUTTER HEALTH, 2005. Asthma - a growing problem. [Web:] http://www.kids.sutterhealth.org/health/asthma.html. [Date of access: 19 Feb. 2005].

TAC ELECTRONIC NEWSLETTER. 2005. Minister of health and the pharmacists - an updated fact sheet on the medicines act and the pricing regulations. [Web:] http://www.tac.org.za/newsletter/2005/ns31_01_2005.htm. [Date of access: 28 May 2005].

TOWNSEND, R.J., BOOTMAN, J.L. & MCGHAN, W.F. 1991. Principles of pharmacoeconomics. United States of America: Harvey Whitney books company. 162p.

UNDEM, B.J. & LICHTENSTEIN, L.M. 2001. Drugs used in the treatment of asthma (*In* Hardman, J.G. & Limbird, L.E., *ed.* The pharmacological basis of therapeutics. New York: Mcgraw-Hill. P.733-755.)

UNIVERSITY ALLIANCE, 2005. Asthma in children and adolescents. [Web:] http://adam.about.com/reports/000005_2.htm. [Date of Access: 8 May 2004].

UNIVERSITY OF CALIFORNIA SAN DIEGO, 1998. Guidelines on diagnosis and asthma management. [Web:] http://meded.ucsd..edu/isp/1998/asthma/html/naep.html [Date of access: 5 Apr. 2004].

UNIVERSITY OF MASSACHUSETTS, 2005. Massachusetts division of medical assistance: drug utilization review program. [Web:] http://www.umassmed.edu/dur/. [Date of access: 2 Apr. 2005.]

VENTURINI, F. & JOHNSON, K.A. 2002. Introduction to pharmacoeconomic principles and applications in pharmacy practice. *Californian journal of health-system pharmacy*, 2: 10-15.

VIRGINIA COMMONWEALTH UNIVERSITY, 2002. How to identify direct costs and facilities and administrative (indirect) costs. [Web:] http://www.vcu.edu/finance/gc-admin/direct-vs-indirect-costs.htm. [Date of access: 27 Apr. 2005].

VOGENBERG, R.F. 2001. Introduction to applied pharmacoeconomics. New York: Mcgraw Hill. 301p.

WEINBERGER, M. 2005. Medication use for asthma. [Web:] http://www.vh.org/pediatric/patient/pediatrics/asthma/04medication.html. [Date of access: 29 May 2004].

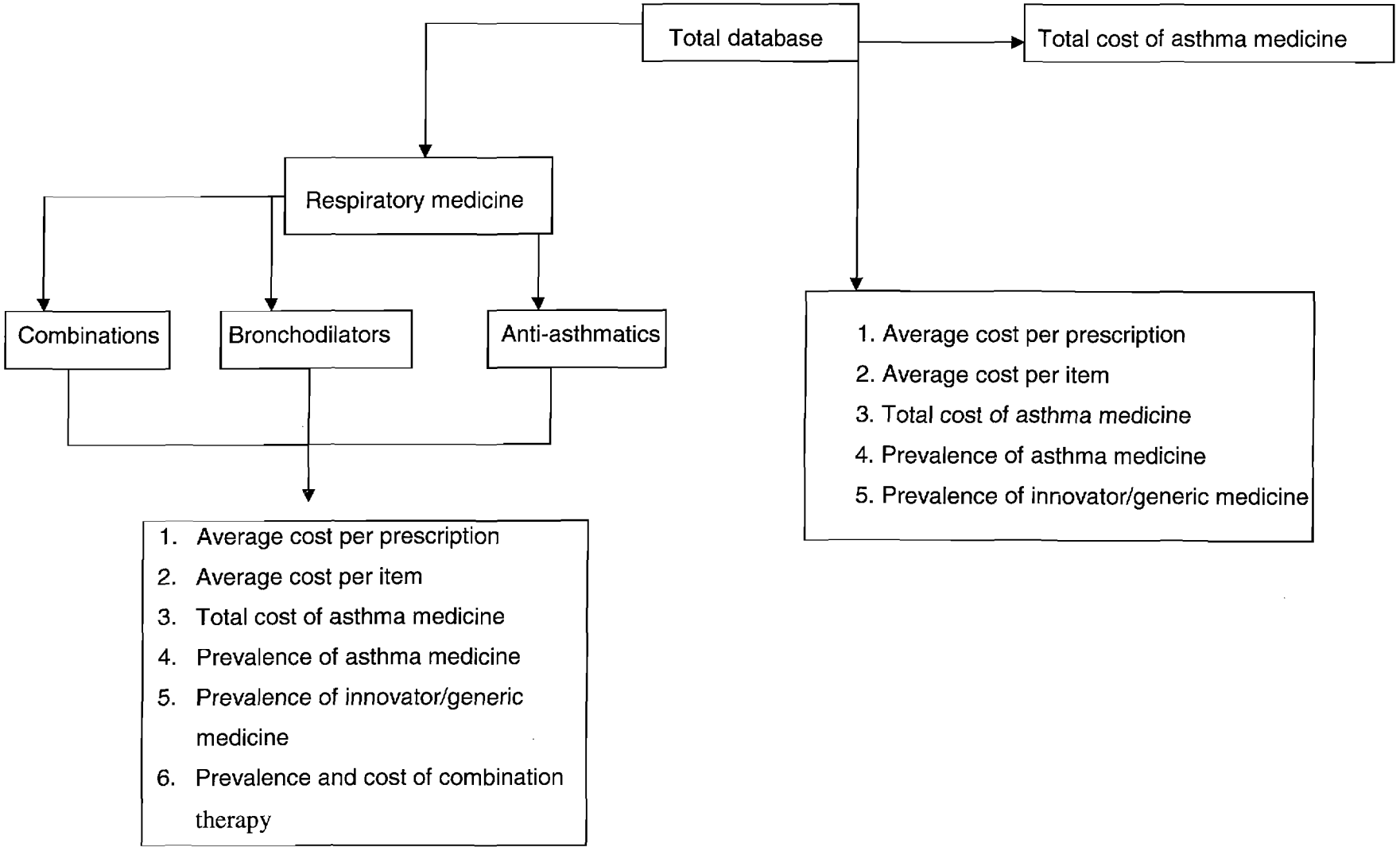
WHITE, T.J. 2001. Making pharmacoeconomics in formulary development a reality. [Web:] http://www.managedcaremag.com/archives/0102/0102.formulary.html. [Date of access: 19 Oct. 2005].

WILLIAMS, S.G., SCHMIDT, D.K. & STORMS, W. 2003. Key clinical activities for quality asthma care: recommendations of the national asthma education and prevention program. [Web:] www.guideline.gov [Date of access: 22 Jun. 2004]

WILSON, L.M. & PRICE, S.A. 2003. Pathophysiology: clinical concepts of disease processes. Elsevier : Mosby. 1200p.

WISCONSIN MEDICAID PHARMACY HANDBOOK. 2001. Drug utilization review omnibus budget reconciliation act of 1990 requirements. [Web:] http://dhfs.wisconsin.gov/medicaid2/handbooks/pharmacy/dur/dur_pc.htm. [Date of access: 8 Apr. 2005].

APPENDIX A


Total database
Total cost of asthma medicine
Respiratory medicine
Combinations
Bronchodilators
Anti-asthmatics
1. Average cost per prescription
2. Average cost per item
3. Total cost of asthma medicine
4. Prevalence of asthma medicine
5. Prevalence of innovator/generic medicine
1. Average cost per prescription
2. Average cost per item
3. Total cost of asthma medicine
4. Prevalence of asthma medicine
5. Prevalence of innovator/generic medicine
6. Prevalence and cost of combination therapy

APPENDIX B

1. Central nervous system
2. Anaesthetics
3. Analgesics
4. Musculo-skeletal agents
5. Autonomic
6. Autacoids
7. Cardio-vascular agents
8. Blood and haemopoeitic
9. Alholism
10. **Respiratory system**
    - **10.1 Coughs and Colds**
    - **10.2 Bronchodilators**
    - **10.3 Mucolytics**
    - **10.4 Anti-astmatics**
    - **10.5 Surfactants**
    - **10.6 Others**
11. Ear, nose and throat
12. Gastro-intestinal tract
13. Anthelmintics
14. Dermatologicals
15. Ophthalmics
16. Urinary system
17. Genital system
18. Anti-microbials
19. Endocrine system
20. Vitamins, tonics, minerals and electrolytes
21. Amino acids
22. Special foods
23. Cytostatics
24. Immunological
25. Chelating agents, ionexchange preparation
26. Biologicals
27. Enzymes
28. Poison antidotes
29. Others
30. Medical gases

APPENDIX C

Table C Generic substitution of innovator products

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Fenoterol			
Berotec® 15ml INH	*	*	*
Berotec® 2.5mg Syr	*	*	*
Berotec® 1.25 UDV SOL	*	*	*
Berotec® 0.5 UDV SOL	*	*	*
Berotec® INH 0.1% SOL	*	*	*
Berotec® Inhalets Cap	*	*	*
Sabax® Fenoterol NF101	*	*	*
Sabax® Fenoterol NF 201	*	*	*
Berotec® 100 15ml Ref	*	*	*
Fluticasone Propionate			
Seretide® 50/250 INH	*	*	*
Seretide® 50/100 INH	*	*	*
Seretide® 50/500 INH	*	*	*
Seretide® 25/125 INH	*	*	*
Seretide® 25/250 INH	*	*	*
Seretide® 50/50 INH	*	*	*
Formoterol			
Oxis® Turbuhaler 9	*	*	*
Foradil® 100 Unit INH	*	*	*
Foradil® Dry+Aerolize	*	*	*
Foradil® 50 Unit INH	*	*	*
Hexoprenaline			
Ipradol® 0.5mg Tab	*	*	*
Ipradol® Syr	*	*	*
Ipradol® 5mcg Amp	*	*	*
Salbutamol			
Ventolin® Accuh INH	*	*	*
Ventolin® 200 INH (N=743)	81.94 (±8.29)	Asthavent® M.D 200 INH (N=6 058) Venteze® Complete INH (N=9 710) Airomir® INH (N= 74)	28.82 (±5.10) 29.86 (±5.13) 86.04 (±17.08)
Ventolin® 300 INH (N=91)	75.41 (±10.82)	Asthavent® M.D 300 INH (N=1 492)	38.02 (±7.19)

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Ventolin® 200 Ref (N=196)	74.35 (±26.57)	Venteze® INH REF (N=443)	22.34 (±15.41)
Ventolin® 300 Ref	*	*	*
Ventolin® 2.5 Nebules	*	*	*
Ventolin® Syr (N=118)	41.71 (±7.99)	Venteze® Syr (N=3 085) Asthavent® Syr (N=1 696)	15.00 (±1.32) 14.12 (±1.91)
Ventolin® Resp Sol (N=34)	109.46 (±14.26)	Venteze® Resp Sol (N=121)	34.56 (±8.65)
Ventolin® 5 mg nebules	*	*	*
Ventolin® Diskhaler	*	*	*
Ventolin® Rotahaler	*	*	*
Volmax® 8mg tab	*	*	*
Volmax® 4mg tab (N=116)	140.40 (±22.97)	Venteze® 4mg Tab (N=816)	28.9 (±5.50)
Salbulin® Autohaler	*	*	*
Cybutol® 400 Cap	*	*	*
Cybutol® 200 Cap (N=13)	34.42 (±11.80)	Asthavent® DP CAP (N=2)	35.66 (± 0.00)
Ventodisk® 400mcg	*	*	*
Salmetarol			
Serevent® 120 INH	*	*	*
Serevent® 60 ACCU INH	*	*	*
Serevent® 60 INH	*	*	*
Terbutaline			
Bricanyl® 0.5bg turbuhaler	*	*	*
Bricanyl® 250mcg Comp	*	*	*
Bricanyl® 250mcg REF	*	*	*
Aminophyllin			
Phyllocontin® TAB	*	*	*
Aminophyllin® 500 2ml	*	*	*
Aminophyllin® 10ml 250	*	*	*
Peterphyllin® 250 AMP	*	*	*
Aminophyllin/Ephedrine			
*Genasma® CAP***	*	*	*
Etafedrine/ Ambuphyllin			
Nethaprin® DOS TAB	*	*	*

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Theophyllin			
Uniphyl® 400mg TAB	*	*	*
Theoplus® 300mg TAB	*	*	*
Rolab-Theophyllin® SR	*	*	*
Euphyllin® Retard TAB	*	*	*
Uniphyl® 600mg TAB	*	*	*
Theoplus® 200mg TAB	*	*	*
Theophen® Elix	*	*	*
Nuelin® SA 250mg TAB	*	*	*
Nuelin® liquid SYR (N=604)	37.19 (±2.41)	Alcophyllin® SYR (N=1 472)	21.46 (±14.25)
Microphyllin® 250 CAP	*	*	*
Pulmophyllin® SR 300	*	*	*
Microphyllin® 125 CAP	*	*	*
Theo-Dur® 300mg TAB	*	*	*
Theo-Dur® 200mg TAB	*	*	*
Chronophyllin® 250 CAP	*	*	*
Nuelin® 125mg TAB	*	*	*
Nuelin® SA 200mg TAB	*	*	*
Nuelin® SA 300mg TAB	*	*	*
Chronophyllin® 375 CAP	*	*	*
Uni-Dur® 400mg TAB	*	*	*
Pulmophyllin® SR 200	*	*	*
Uni-Dur® 600mg TAB	*	*	*
Theophyllin/Ephedrine			
Norstan® TED 200mg	*	*	*
Norstan® TED 300mg	*	*	*
Theophyllin/Etophyllin			
Solphyllin® SYR	*	*	*
Fenoterol/Ipratropium			
Atrovent® Beta UDV	*	*	*
Ipratropium			
Atrovent® 0.25mg UDV (N=829)	78.27 (±28.68)	Sabax® Ipratropium NI101 (N=33)	62.30 (±28.79)
Atrovent® MDI 300 Dose	*	*	*
Atrovent® 0.5mg UDV (N=483)	164.88 (±60.60)	Sabax® Ipratropium NI201 (N=15)	182.44 (±64.89)
Atrovent® SOL	*	*	*
Atrovent® 40 Inhalets (N=7)	151.13 (±39.19)	Ipvent® 40 200D INH (N=460)	90.77 (±12.05)
Budesonide/Formoterol			

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Symbicord® Turbo 120	*	*	*
Symbicord® Turbo 60 D	*	*	*
Fenoterol/Ipratropium			
Duovent® MAV 300 Dose	*	*	*
Berodual® MDI 200	*	*	*
Duovent® Complete INH	*	*	*
Sabax® Nebrafen 4ml	*	*	*
Ipratropium/Salbutamol			
Combivent® UDV SOL	*	*	*
Combivent® MDI INH	*	*	*
Tiotropium			
Spiriva® MA Refill CPS	*	*	*
Spiriva® MA Complete Kit	*	*	*
Beclomethasone			
Beclate® 200mcg INH	*	*	*
QVAR AUTOHALER 100	*	*	*
Becotide® 100 INH (N=213)	120.60 (±22.03)	Beclate® 100mcg INH (N=1 513) QVAR® INH 100 (N=495) Beceze® 100mcg INH (N=29)	123.44 (±17.53) 216.23 (±28.59) 123.19 (±54.45)
Becotide® 100 REF	*	*	*
Becloforte® 200 INH	*	*	*
QVAR® Autohaler 50	*	*	*
Becotide® Rota 200mcg	*	*	*
Becotide® 50 REF	*	*	*
Becotide® 50 INH (N=56)	70.09 (±18.88)	Beclate® 50mcg INH (N=433) QVAR® 50 INH (N=39) Beceze® 50mcg INH (N=3) Ventzone® INH (N=2)	65.77 (±10.12) 127.87 (±23.25) 80.56 (±0.11) 108.51 (±R0.00)
Becodisk® 200mcg BLIST	*	*	*
Becodisk® 100mcg BLIST	*	*	*
Aerobec® 100 Autohaler	*	*	*
Aerobec® 50 Autohaler	*	*	*

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Aerobec® Forte Autohaler (N=6)	370.30 (±88.71)	Clenil® Aerosol INH (N=122) Beceze® 250mcg INH (N=22)	59.36 (±15.15) 255.99 (±14.86)
Cyclosan® CAP	*	*	*
Becotide® Rota 100mcg	*	*	*
Becotide® Diskhaler	*	*	*
Budesonide			
Budeflam® 200/300 GEN	*	*	*
Inflammide® 200 Mac (N=5 689)	212.23 (±27.84)	Budeflam® MET 200mcg (N=8)	167.96 (±9.56)
Inflammide® 100 Mac (N=2 224)	154.39 (±15.72)	Budeflam® MET 100mcg (N=7)	154.00 (±0.00)
Pulmicort® Turbo 200	*	*	*
Pulmicort® 200ug INH	*	*	*
Pulmicort® 0.25mg UDV	*	*	*
Pulmicort® 0.5mg UDV	*	*	*
Inflammide® 200 I/SYS	*	*	*
Inflammide® 100 I/SYS	*	*	*
Inflammide® 50 MAC	*	*	*
Pulmicort® 100ug INH (N=485)	171.70 (±21.27)	Budeflam® 100/300 GEN (N=2 135)	170.96 (±9.33)
Pulmicort® TURBO 100	*	*	*
Pulmicort® TUR400/100	*	*	*
Pulmicort® 50ug	*	*	*
Pulmicort® TUR 400/50	*	*	*
Budeflam® 100/300 ZER	*	*	*
Budeflam® 100mcg 300	*	*	*
Inflacor® 400mcg CPS	*	*	*
Fluticasone			
Flixotide® 250 ACCINH	*	*	*
Flixotide® 250 CFC INH	*	*	*
Flixotide® 125 CFC INH	*	*	*
Flixotide® 100 ACC INH	*	*	*
Flixotide® 50 INH	*	*	*
Flixotide® 250 INH	*	*	*
Flixotide® 500 ACC INH	*	*	*
Flixotide® 125 INH	*	*	*
Flixotide® 50 ACC INH	*	*	*
Flixotide® 25 INH	*	*	*
Montelukast			
Singulair®	*	*	*
Singulair® 10mg FC TB	*	*	*

Innovator products	Average price of innovator product (R)	Generic substitution	Average price of generic product (R)
Singulair® 5mg CH TAB	*	*	*
Zafirlukast			
Accolate® 20 TAB	*	*	*
Ketotifen			
Zaditen® 1mg TAB	*	*	*
Zaditen® SRO TAB	*	*	*
Zaditen® 1mg/5ml SYR	*	*	*
Zaditen® Oral INF DRP	*	*	*
Ketohexal® 200ml SYR (N=409)	62.15 (±5.82)	Zetofen® 200ml SYR (N=534) ADCO-Ketotifen SYR (N=374)	65.99 (±10.20) 55.95 (±5.25)

APPENDIX D

Asthma Questionnaire (American academy of allergy of allergy and immunology, 2002).

1. When I walk or do simple chores, I have trouble breathing or I cough.	Yes ___ No ___
2. When I perform heavier work, such as walking up hills and stairs or doing chores that involve lifting, I have trouble breathing or I cough.	Yes ___ No ___
3. Sometimes I avoid exercising or taking part in sports like jogging, swimming, tennis or aerobics because I have trouble breathing or I cough.	Yes ___ No ___
4. I have been unable to sleep through the night without coughing attacks or shortness of breath.	Yes ___ No ___
5. Sometimes I can't catch a good, deep breath.	Yes ___ No ___
6. Sometimes I make wheezing sounds in my chest.	Yes ___ No ___
7. Sometimes my chest feels tight.	Yes ___ No ___
8. Sometimes I cough a lot.	Yes ___ No ___
9. Dust, pollen or pets make my breathing more difficult.	Yes ___ No ___
10. Cold weather makes my breathing more difficult.	Yes ___ No ___
11. My breathing problem gets worse when I'm around tobacco smoke, fumes or strong odors.	Yes ___ No ___
12. When I catch a cold, it often goes into my chest.	Yes ___ No ___
13. I had one or more emergency visits to a doctor in the last year because of breathing problems.	Yes ___ No ___
14. I had one or more overnight hospitalizations due to breathing problems in the last year.	Yes ___ No ___
15. My breathing problem controls my life more than I would like.	Yes ___ No ___
16. I feel tension or stress because of my breathing problems.	Yes ___ No ___
17. I worry that my breathing problem effects my health or may even shorten my life.	Yes ___ No ___
Answer the following if you currently are taking asthma medication:	
18. I feel like I use my asthma inhaler too often.	Yes ___ No ___
19. Sometimes I don't like the way my asthma medicine(s) makes me feel.	Yes ___ No ___
20. My asthma medicine(s) doesn't control my asthma.	Yes ___ No ___