The treatment of paediatric asthma in the private health care sector of South Africa: A retrospective drug utilisation review

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"Do more than exist, *live*. Do more than touch, *feel*. Do more than look, *observe*. Do more than read, *absorb*. Do more than hear, *listen*. Do more than listen, *understand*. Do more than think, *ponder*. Do more than talk, *say something*".

John H. Rhoades

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ABSTRACT

Title: The treatment of paediatric asthma in the private health care sector of South Africa: A retrospective drug utilisation review

Keywords: asthma, paediatric asthma, drug utilisation review, prescribing patterns, prevalence, South Africa.

Asthma is the most common chronic disease among children worldwide. The prescribing patterns of the medication used to treat asthma in South Africa, as well as the prevalence of paediatric asthma are of interest and need to be investigated.

A drug utilisation review was performed to determine the prevalence of asthma, and in particular paediatric asthma in a section of the private health care sector of South Africa. The prescribing patterns of asthma medication were investigated according to different demographic factors, such as gender, geographical area and prescriber type. Data from a medical claims database were extracted and processed to reveal the different prescribing patterns from 1 January 2005 to 31 December 2008. Medication from the MIMS® pharmacological groups 10.2 and 10.4 were used as a basis for asthma medication. Patients had to use at least one medicine item from one of these groups to be included in the study.

The prevalence of asthma in the general population showed an increase from 2005 to 2008. The prevalence of asthma as a part of the total database according to the number of patients increased from 23.01% in 2005 (n=347342) to 24.72% in 2008 (n=240854), although the number of patients on the total database decreased from 2005 to 2008. When investigating the number of prescriptions that were dispensed during 2008, asthma prescriptions comprised 7.16% (n=484983) of all prescriptions and the number of asthma medicine items that were dispensed made up 3.72% (n=611139) of the total number of medicine items dispensed in 2008.

Paediatric asthma was divided into two age groups for the purpose of this study namely, 0 – 4 years of age and older than 4 years, but younger or equal to 11 years of age (>4 ≤ 11 years), according to a previous study done by the National Heart Lung and Blood Institute (NHLBI). The results from the data confirmed that the prevalence of asthma was higher in the younger age group. The number of patients using asthma medication in the 0 – 4 years age group comprised 44.40% (n=11306) of the total number of patients in this age group on the database in 2008, compared to 32.84% (n=28347) in the >4 ≤ 11 years age group. Asthma was more common among male patients, whether they were included in the paediatric groups or not. The geographical distribution of paediatric asthma seemed to be connected to the provinces without coastlines and different mining facilities. The combination

of asthma medication with antibiotics and systemic corticosteroids were investigated and it was concluded that antibiotics that were used for respiratory tract infections were prescribed the most frequently to asthma patients.

The refill-adherence rates of patients with asthma were not satisfactory when considering that asthma is a chronic disease. The average adherence rate for all the asthma products that were brought into account when calculating the refill-adherence rate was 60.95%. A rate above 90% indicates optimal patient adherence.

In conclusion this study determined that asthma has a significant prevalence among children in South Africa. The prescribing patterns for the different medication used in the treatment of asthma were investigated and recommendations for further research in this field of study were made.

OPSOMMING

Titel: Die behandeling van pediatriese asma in die privaat gesondheidsorgsektor in Suid-Afrika: ‘n Retrospektiewe medisyneverbruikstudie

Sleutelwoorde: asma, pediatriese asma, medisyneverbruikstudie, voorskryfpatrone, voorkoms, Suid-Afrika.

Asma is wêreldwyd die algemeenste chroniese siekte wat onder kinders voorkom. Die voorskryfpatrone van die verskillende medisyne wat gebruik word om asma te behandel, asook die voorkoms van pediatriese asma in Suid-Afrika is belangrik en regverdig ‘n ondersoek.

‘n Retrospektiewe medisyneverbruikstudie is uitgevoer om die voorkoms van asma en veral pediatriese asma in ‘n gedeelte van die private gesondheidsorg stelsel in Suid-Afrika te bepaal. Die voorskryfpatrone van die medisyne wat gebruik word om asma te behandel is volgens verskillende demografiese parameters, soos geslag, geografiese gebied en kategorie voorskrywer, bv. pediater, pulmonoloog of algemene praktisyn, ondersoek. Data is vanaf ‘n mediese eise databasis, verkry. Die data is verwerk om voorskryfpatrone vanaf 1 Januarie 2005 tot 31 Desember 2008 te bepaal. Die medisyne wat gebruik is vir die behandeling van asma is geklassifiseer onder farmakologiese groepe 10.2 en 10.4 van die MIMS® klassifikasie sisteem. Pasiënte wat by die studie ingesluit is, moes ten minste een medisyne item wat onder een van die groepe klassifiseer, gebruik het.

Die voorkoms van asma in die studie populasie het van 2005 tot 2008 toegeneem. Volgens die aantal pasiënte uit die totale databasis wat asma medikasie gebruik het, het die voorkoms van asma toegeneem van 23.01% in 2005 (n=347342) tot 24.72% in 2008 (n=240854), alhoewel die aantal pasiënte op die totale databasis afgeneem het van 2005 tot 2008. Uit die aantal voorskrifte wat gedurende 2008 geresepteer is, het asma voorskrifte 7.16% (n=484983) van alle voorskrifte uitgemaak. Asma medikasie items (n=611139) het 3.72% verteenwoordig van die totale aantal items geëis in 2008.

Pediatriese asma was vir die doel van hierdie studie in twee ouderdomsgroepe verdeel, naamlik 0 – 4 jaar en ouer as 4 jaar, maar jonger of gelyk aan 11 jaar (>4 ≤ 11 jaar). Die indeling is gedoen volgens ‘n studie wat verneem is deur die *National Heart Lung and Blood Institute* (NHLBI). Die resultate wat uit die data verkry is, het bevestig dat die voorkoms van asma hoër was in die jonger ouderdomsgroep. Die aantal pasiënte in die 0 – 4 jaar ouderdomsgroep wat asma medisyne gebruik het, het 44.40% (n=11306) van die totale aantal pasiënte in die ouderdomsgroep beslaan, teenoor 32.84% (n=28347) in die >4 ≤ 11

jaar ouderdomsgroep. Asma het ook ‘n hoër voorkoms getoon onder manlike pasiënte in die pediatriese ouderdomsgroepe, sowel as in die volwassene ouderdomsgroep. Die geografiese verspreiding van pediatriese asma hou dalk verband met provinsies wat nie aan die kus grens nie en provinsies waar mynbou volop is. Asma medisyne in kombinasie met antibiotika en sistemiese kortikosteroïede is ondersoek. Die gevolgtrekking was dat antibiotika wat gebruik word teen respiratoriese infeksies meeste aan asma pasiënte voorgeskryf is.

Die frekwensie waarteen pasiënte hul voorskrifte herhaal en die gebruiksaanwysings getrou nakom was volgens die resultaat van die studie onbevredigend en het op swak pasiënt meewerkendheid gedui. Dit is veral ‘n belangrike bevinding omdat asma ‘n chroniese siektetoestand is. Die gemiddelde hervullingskoers vir al die asma produkte wat in berekening gebring is, was 60.95% waar ‘n waarde van bo 90% verwag word vir voldoende meewerkendheid.

Hierdie studie het bevestig dat asma wel ‘n beduidende voorkoms onder kinders in Suid-Afrika het. Die voorskryfpatrone van die verskillende medisyne wat ondersoek is en aanbevelings vir verdere navorsing in die rigting is gemaak.

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CHAPTER 1

Introduction

1.1 Introduction

This dissertation will focus on the treatment of asthma, with special reference to paediatric asthma according to a medicine claims database of a pharmaceutical benefit management company. The treatment of asthma as well as the important issues surrounding the disease will be discussed. Some research questions will be formulated and general and specific objectives for the study will be set. The research method will be discussed shortly and the division of the following chapters will be mentioned.

1.2 Asthma treatment overview

Asthma is a chronic disease that is responsible for inflammation of the airways. This inflammation leads to "airway hyper-responsiveness, airflow limitation and respiratory symptoms" (Lundbäck *et al.*, 2009:349). It is an incurable disease, but responds well to treatment. Asthma medication can be classified into two main groups according to the American Academy of Allergy Asthma and Immunology (AAAAI) (2007). In the MIMS® (Snyman, 2009a:14a) asthma medication is classified as groups 10.2 and 10.4. The first group provides quick relief in case of an asthma attack. This group includes the bronchodilators. The effects of the bronchodilators are only temporary and ensure relief of symptoms. Drugs in this group are the bronchodilators and oral corticosteroids. The second group includes long-term medications used to control inflammation in the airways and prevent attacks in patients that suffer from asthma. They are called the anti-asthmatics. Medicines used for this purpose are the inhaled corticosteroids, cromolyn or nedocromil, leukotriene modifiers, inhaled long-acting beta-2 agonists, methylxanthines and omalizumab (AAAAI, 2007). These products can be classified according to the World Health Organization's (WHO) ATC (Anatomical Therapeutic Chemical) classification system into group R 03 (R: respiratory system, 03: drugs for obstructive airway diseases) (WHO, 2009a).

1.3 Problem statement

According to studies done by Serfontein (1996:118) and Kilian (2005:100), asthma has a significant prevalence in the South African society. Kilian (2005:100) discovered that 4.46% of all prescriptions claimed through a pharmacy benefit management company (PBM) were for asthma medication. Serfontein (1996:118) found that 12% of chronic patients on the prescribing claims database were affected by asthma in 1996.

The WHO (2008) calculated that 300 million people globally suffer from asthma and according to the American Lung Association's Asthma and Children fact sheet (American Lung Association, 2010), asthma affects 7.1 million children under 18 years in the Unites States. This makes asthma the most common chronic disease in children. Asthma should not only be seen as a disease that affects many people, it is also a very dangerous disease. The mortality rate for asthma in South Africa is as high as 77.643 deaths per 1 million people (NationMaster, 2004). This makes South Africa the country with the second highest mortality rate for asthma in the world. In the United States, deaths due to asthma are not common in children. The number of deaths does however increase with age. In 2004, 131 asthma deaths were among children under 15 years, whereas 653 deaths occurred among adults aged 85 years and older (American Lung Association, 2010).

Asthma treatment has its problems. The bronchodilators (selective $beta_2$ agonists) have side-effects such as tremors, palpitations and tachycardia and also hypertrichosis with chronic use. Inhaled glucocorticoids can cause orophararyngeal candidiasis and laryngeal myopathy. The methylxanthines lead to serious adverse effects such as gastric irritation and other gastric effects and it also stimulates the central nervous system and may lead to insomnia, tremors and very important, convulsions (Rossiter, 2010:536).

All the above-mentioned effects cause a decrease in patient adherence. Patients that are adherent can, according to the Mediscor Medicine Review: 2007 (Bester & Hammann, 2008:20), be considered as "patients that used more than 80% of their medicine". Thus, they get their prescription filled 10 times or more during a period of twelve months. Asthma is listed as one of the 27 diseases on the Chronic Disease List as indicated by the Medical Scheme Act 1998 (Act 131 of 1998) (South Africa, 2002:30). In 2007 only 29.8% of patients receiving chronic asthma treatment were adherent according to the Mediscor's study on the Chronic Disease List. This makes asthma the disease with the second worst adherence, only after haemophilia (16.7%) (Bester & Hammann, 2008:21). This result must be seen in the context of the treatment, because patients often do not use their inhalers for only one month, particularly if they do not use their preventative medication as prescribed (Bester & Hammann, 2008:20).

Another factor that could influence the patient adherence is the cost of the medicine. Asthma can be classified as a relatively expensive disease. Costs relating to asthma can be direct costs such as medication and hospitalisation costs, pharmacy costs or indirect costs like absenteeism because of asthma. In the United States the total cost of asthma is estimated at $14 billion and in Australia at $800 million each year (Edwards, 2004:60). Drugs that were used in the treatment of asthma were responsible for the highest single direct cost at $5.9 billion in the United States (American Lung Association, 2010). Asthma is also currently one of the leading causes of hospitilisation and school absenteeism in children according to the

American Lung Association (2010). The above information indicates that there are problems with asthma treatment and adherence in children and there is room for a study to determine the prescribing patterns, prevalence and costs involving asthma in the private health care sector of South Africa.

1.4 Research Questions

The following research questions were formulated:

- What is the prevalence of asthma and especially paediatric asthma in South Africa?
- What do the prescribing patterns of asthma medication in South Africa entail?

1.5 Research Objectives

This study contains a general objective as well as some specific objectives.

1.5.1 General objective

The general objective of the study was to determine the prescribing patterns of asthma products in South Africa with special reference to children aged 11 years and younger.

1.5.2 Specific objectives

The specific objectives can be divided into literature study objectives and empirical study objectives.

1.5.2.1 Literature study objectives

The literature objectives were as follows:

- To describe and define asthma, the different types of asthma, its diagnosis, treatment and treatment guidelines.
- To describe the prevalence of asthma and according to demographical factors such as age, gender and geographical area in South Africa and other countries.
- To determine the patients' adherence to their asthma medication as well as the economic burden that asthma has on patients.

1.5.2.2 Empirical study objectives

The empirical study objectives were as follows:

- Determine the prevalence of asthma in a section of the private health care sector of South Africa according to various demographical factors such as age and gender.

- Determine the prescribing patterns and cost of asthma medication according to therapeutic category, active ingredient and trade name.
- Determine the prevalence of asthma in children according to gender and geographical area in a section of the private health care sector.
- Determine the costs associated with paediatric asthma medication in a section of the private health care sector of South Africa.
- Investigate the prescribing patterns of asthma medication to paediatric patients according to gender, therapeutic category, active ingredient, trade name and prescriber (general practitioners, pulmonologists and paediatricians).
- To review the prevalence of the prescribing of antibiotics and/or systemic corticosteroids together with asthma therapy.
- Investigate the paediatric patients' refill-adherence rate to certain asthma medication.

1.6 Research Method

This study consists of two main parts:

- Literature study
- Empirical research study

1.6.1 Phase 1: Literature study

The literature study focuses on asthma as a chronic disease as well as certain aspects like childhood asthma. The diagnoses, symptoms, treatment and treatment guidelines will be discussed. Determining the prevalence of asthma according to demographical factors will be one of the goals. Patient adherence is an important aspect of asthma treatment and needs to be reviewed.

1.6.2 Phase 2: Empirical research study

The empirical study involves the procurement of data and analysing the data to show the results of the study. Certain conclusions are then drawn and recommendations are made.

1.6.2.1 Research design

A retrospective drug utilisation review (DUR) was performed. According to Brodie and Smith (quoted by Guo *et al.*, 1995:1175) DUR can be defined as "an authorized, structured, and continuing program [*c*] that reviews, analyses, and interprets patterns [rates and costs] of drug usage in a given health care delivery system against predetermined standards." Guo *et*

al. (1995:1175) further state that the primary goal of DUR is to monitor prescribing patterns, identify inappropriate prescribing and minimise drug costs through review processes that can be prospective, concurrent or retrospective.

1.6.2.2 Data source

The data for this study were extracted from a medicine claims database of a PBM in South Africa. The data obtained were for a period of four years from 1 January 2005 to 31 December 2008. The data were analysed in periods of 12 months at a time.

1.6.2.3 Study population

An asthma study population had to be compiled out of the total database. The total database contained the following information:

Table 1.1: General prescribing patterns of the total database for the years 2005 to 2008.

Year	Total number of patients	Total number of prescriptions	Total number of medicine items	Total expenditure on medicine items (R)
2005	1509621	8391836	19500774	1 819 865 251.63
2006	1558090	8906348	21113422	1 959 738 734.09
2007	1178596	7911096	19075724	1 918 284 176.00
2008	974497	6775873	16439253	1 785 871 013.85

The asthma study population was composed in the following manner:

- Patients that had used medication for asthma as classified by MIMS® groups 10.2 (bronchodilators) and 10.4 (anti-asthmatics) (Snyman, 2009a:14a). It was essential that patients had to use at least one type of medication from any one of these groups.
- Patients that fall under the following age groups were used to determine the paediatric asthma population:
  - ❖ 0 – 4 years
  - ❖ > 4 ≤ 11 years

Patients that were older than 11 years were considered as adults and not included in the paediatric study population.

1.6.2.4 Editing and coding of data

The following measuring instruments were used to edit the data and draw conclusions:

- The NAPPI code
- The MIMS® classification system
- Age
- Gender
- Prescriber type
- Geographical area
- Prevalence
- Cost

1.7 Division of chapters

Chapter 1: Introduction

Chapter 2: An overview of asthma

Chapter 3: Research methodology

Chapter 4: Results and discussion

Chapter 5: Conclusions and recommendations

Chapter 6: Bibliography

1.8 List of abbreviations

The following abbreviations and acronyms were used for the purpose of this study:

β_2 – agonist: Beta-2 receptor agonist

AR: Refill-adherence rate

ATC: Anatomical therapeutical chemical index

DUR: Drug utilisation review

FEV_1: Forced expiratory volume in one second

GINA: Global initiative for asthma

GORD: Gastro-oesophageal reflux disease

IgE: Anti-immunoglobulin E

IV: Intravenous route of administration

LABA: Long-acting β_2-agonist

MDI: Metered dose inhaler

MIMS®: Monthly Index of medical specialities

NAPPI: National pharmaceutical pricing index

NHLBI: National heart lung blood institute

PBM: Pharmaceutical benefit management

PEFR: Peak expiratory flow rate

UDV: Unit dose vial

1.9 Chapter summary

This chapter served as an introduction for the rest of the dissertation. The problems with asthma as well as facts about asthma were discussed. The research objectives as well as the research design that was followed were mentioned. Furthermore, the division of the chapters can be seen. In the next chapter an overview of asthma as a disease will be given.

CHAPTER 2

An overview of asthma

2.1 Introduction

In this chapter asthma as a disease will be discussed. The diagnosis, treatment and treatment guidelines of asthma are important and need to be discussed to understand asthma. Further, the prevalence of asthma, which is imperative to this study, will be discussed in terms of the patient's age, gender and geographical location. Patient refill adherence is also an important part of asthma therapy and must be reviewed.

2.2 Definition of asthma

According to the WHO (2009c) asthma can be defined as a chronic disease that is typified by frequent attacks of breathlessness and wheezing. Individual attacks differ in severity and frequency and could occur at longer intervals or daily or even hourly (WHO, 2009c). Inflammation of the airways plays a key role in asthma. It affects the nerve endings in the airways and leads to irritation that causes the lining of the air passages to swell. The swelling then causes the airways to constrict and reduces airflow in and out of the lungs (WHO, 2009c).

The Global Initiative for Asthma (GINA) identifies asthma as a disease that leads to respiratory problems and presents with symptoms such as breathlessness, wheezing, a tight chest and coughing. The airways are hyper responsive to changes and stimuli from the environment and an asthma attack can easily be triggered (GINA, 2004).

The National Heart Lung and Blood Institute's (NHLBI) Expert Panel Report 3 on guidelines for the diagnosis and management of asthma (NHLBI, 2007:12) defined asthma as a complex disease that affects the airways and has variable and recurring symptoms, including airflow obstruction and bronchial hyper responsiveness. The underlying inflammation of the airways is a key feature of clinical asthma (NHLBI, 2007:12).

Rees and Price (1989:1) said that it was the reversibility of airflow characterised by wide deviations over short periods of time. A characteristic of asthma is that bronchoconstriction occurs in reaction to stimuli and bronchodilation will manifest when treatment is administered.

2.3 Diagnosis of asthma

Asthma is a disease that is not easily diagnosed. It is a complex disease and could be fatal if it is not identified and treated properly. The problem is that asthma is often under-diagnosed and the severity thereof is repeatedly under-assessed (Rance, 2008:255). Diagnosis of asthma plays an important part, but is only the first step to control asthma and better the patient's quality of life. According to NHLBI (2007:40) methods to establish a diagnosis of asthma include the following:

- Taking a detailed medical history of the patient.
- Doing a physical examination of the patient. Special attention is paid to the upper respiratory tract, the skin and the chest.
- Spirometry - it assesses the obstruction of the airways and determines the reversibility of the obstruction.
- Excluding differential diagnoses.

To confirm the diagnosis of asthma the clinician must be certain that the patient experiences symptoms of airflow obstruction or hyper responsiveness of the airways, that the obstruction in the air passages are at least reversible to some extent and that all alternative diagnoses had been excluded.

The process of making an asthma diagnosis consists of a number of activities (NHLBI, 2007:41):

First the physician will ask a number of questions about the patient's medical background and also ask the patients what symptoms they are experiencing and what allergens they might have been exposed to. A physical examination of the patient will follow, to determine whether the patient wheezes on expiration. This sign is usually associated with asthma, but is not specific to asthma. Spirometry or pulmonary function testing may be performed on the patient, because the medical history and a physical examination may not be sufficient resources to exclude differential diagnosis or to determine the extent of lung function impairment (NHLBI, 2007:43).

Asthma can be diagnosed by a number of objective diagnostic tests:

- The peak expiratory flow rate is measured by exhaling into a simple apparatus with force. The patients can do this at home if they have a peak flow meter (Rees & Price, 1989:2). A chart can be used to determine the normal values accounting for the patient's gender, age and height (Davis *et al*., 2000:155). A plan needs to be

implemented if a patient's peak flow is below 80% of the normal reading (Bass, 2009a).

- Spirometry is used often to determine lung function. It is similar to peak flow, but the apparatus is more advanced and a physician usually performs this test (Bass, 2009b). The severity of the patient's weak lung function and airflow obstruction can be determined through spirometry. The benefit of a spirometry meter is that it can be used to distinguish between obstructive and restrictive lung diseases as well (Murphy, 2007:21). A physician can also test for asthma by administration of a bronchodilator. Spirometry would be performed on a patient without a bronchodilator and the value noted. The physician will then treat the patient with a bronchodilator that will provide quick relief. After 10 to 15 minutes another spirometry test will be performed again. If the value shows a significant increase in airflow of 15%, then a diagnosis of asthma can be considered and can aid in making a final diagnosis (Rees & Price, 1989:3; Murphy, 2007:101). Spirometry is valuable in children older than five years of age, as the action has to be done correctly (NHLBI, 2007:43).

- Bronchoprovocation or bronchial hyper responsiveness can be used to test for asthma (NHLBI, 2007:45; Murphy, 2007:22). The patient is exposed to an allergen or an irritating substance, such as histamine or metacholine, to see whether airflow obstruction takes place. In children it is preferred that exercise provocation is used, because it is better tolerated and a more natural way to induce bronchoconstriction. Approximately 90% of asthmatic children will test positive when they have to exercise (Rees & Price, 1989:3). This test is not performed often, only when patients present with symptoms that are atypical, and it is carried out by a trained professional (Murphy, 2007:22). A positive bronchoprovocation test does not necessarily mean that the patient has asthma. Allergic rhinitis, cystic fibrosis and chronic obstructive pulmonary disease deliver positive results with bronchoprovocation as well. A negative result will help to rule out asthma (NHLBI, 2007:45).

- Blood and sputum tests and skin-prick tests are used to investigate atopic symptoms. These tests are used in allergy testing, but many patients with asthma are atopic and experience a reaction to a number of allergens, that could be an exacerbation of an asthma attack (NHLBI, 2007:167; Murphy, 2007:23). IgE antibodies and eosinophil concentrations are measured, which are usually present in the case of an allergic reaction (Rees & Price, 1989:4). These tests are not necessary to make a diagnosis of asthma, nor are they particularly useful (Murphy, 2007:23).

- X-rays are not used often in asthma diagnosis, because the chest x-ray seems normal in asthma patients, but it could be useful when a patient's asthma has been

under-diagnosed for a period of time. The x-rays will then show signs of hyperexpansion of the lung (Bass, 2009a). In acute exacerbations definite hyperinflation of the lungs can be observed (Murphy, 2007:24). The use of chest x-rays is limited and is more useful to exclude certain differential diagnoses, such as pneumothorax (Murphy, 2007:25). All patients with atypical symptoms should, however, receive a chest x-ray (British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN), 2003:i5).

2.3.1 Types of asthma

Asthma can be classified into five different types: allergic, non-allergic, exercise-induced, occupational and nocturnal asthma (AAAAI, 2010).

- ***Allergic asthma***

Allergic asthma is usually triggered by allergens and irritants, such as dust, pollen and animal dander. It is also known as extrinsic or atopic asthma (Murphy, 2007:13). It is associated with the obstruction of the airways due to allergies. Approximately 60% of cases worldwide are allergic asthma (AAAAI, 2010).

- ***Non-allergic asthma***

The cause of non-allergic asthma or intrinsic asthma is usually viral infections (colds and viral pneumonia) or medications such as aspirin that can induce an attack (Murphy, 2007:13). Gastro-oesophageal reflux disease (GORD) may also lead to this type of asthma and irritants, airborne particles and pollutants are triggers. A third of all patients with asthma suffer from non-allergic asthma (AAAAI, 2010).

- ***Exercise-induced asthma***

This type of asthma occurs only when the patient exercises, but it should be expected in all asthma patients (Boguniewicz *et al*., 2009:1032). Exercise-induced asthma should not be confused with asthma that is not controlled and precipitate as a result of exercise (Rossiter, 2010:532). Strenuous physical activity and breathing in cold, dry air while exercising triggers exercise-induced asthma. The degree of the asthma attack varies between patients and could be serious or mild. Up to 80% of patients with asthma will experience symptoms of an attack during exercise and around 35% of patients with seasonal allergies experience exercise-induced asthma, with worsening symptoms in autumn and spring (AAAAI, 2010).

- ***Occupational asthma***

This type of asthma can be directly traced back to the patient's working environment. If a patient is working in an area where he or she is exposed to harmful gases, fumes, chemicals

or metals in a mine or factory for example, there is a chance that he/she might develop asthma because of it (AAAAI, 2010). Occupational asthma should not be confused with work-aggravated asthma, which is pre-existing asthma that is exacerbated by the work environment of the patient (Murphy, 2007:14). Prevention would be the best way to treat this type of asthma, but if that is not possible, the patient should consider wearing a mask to filter out the causative agent or try to alter the working conditions to minimise exposure (Rees & Price, 1989:10).

- ***Nocturnal asthma***

This type of asthma is also known as sleep-related asthma, because it occurs when the patient is sleeping despite the time of day. It could occur due to temperature changes in the body, allergen exposure or a delayed effect, GORD or a decrease in circulation of adrenal gland hormones (Calhoun, 2003:404S). Nocturnal asthma is quite common and occurs in up to 75% of asthma patients (AAAAI, 2010). Nocturnal asthma is usually the result of poorly controlled asthma and presents at night. These patients should be put on adequate controller therapy (Rossiter, 2010:532).

2.3.2 Diagnosis of asthma in children

According to the Pediatric Dosage Handbook (Taketomo *et al*., 2000:15) a child is defined as follows:

Table 2.1: The classification of paediatric patients according to age

Infant	1 month to 1 year of age
Child/Children	1 – 12 years of age
Adolescent	13 – 18 years of age

For the purpose of this study, a child's age will be defined as a person between the ages of 0 – 11 years of age, according to the guidelines for the treatment of asthma by the NHLBI. This age group will be divided into two smaller groups, the first ranging from 0 – 4 years of age and the second from 4 – 11 years of age (NHLBI, 2007:72).

The diagnosis of asthma in children can be difficult (BTS/SIGN, 2003:i6). There are two sides to the diagnosis of asthma in children. Both have important implications in the way asthma is perceived. Firstly asthma can be under-diagnosed, especially in children between one month and four years (NHLBI, 2007:281). The disease is then falsely labelled as either chronic and wheezing bronchitis, reactive airway disease, recurring pneumonia, gastro-esophageal reflex or upper respiratory tract infections (NHLBI, 2007:281). This leads to children not receiving adequate therapy to control their asthma. Clinicians are careful to use

the word “asthma” when dealing with paediatric patients. This may be to avoid parental concern, but it is actually an obstruction to the correct treatment of the child and leaves the parents without a rational explanation of their child’s condition. Often only bronchitis is diagnosed and treated, while the wheezing of the child is ignored. This can be very dangerous, because the patient is not receiving adequate treatment and parents will not think of calling an ambulance for bronchitis or a tight chest (Speight *et al*., 1983:1255). Over-diagnosis can also occur, because not all wheezing and coughing necessarily would mean the child is suffering from asthma. Respiratory illnesses are a normal aspect of childhood and do not always need medication (Keeley & Silverman, 1999:627). Over-diagnosis in the general population is occurring as well (Linden-Smith *et al*., 2004:103). In a Canadian study it was found that 41% of patients that were labelled as asthmatics did not show reversible airflow obstruction and did not test positive when a metacholine test was performed (Linden-Smith *et al*., 2004:103). This would lead to unnecessary use of medication and greater medical costs. Care must therefore be taken to confirm that the patient positively has asthma through spirometry and bronchoprovocation. What makes diagnosis between the ages of one month to four years even more difficult are the measurements of lung function that are not always considered objective. Children between the ages of 5 and 11 years have the same criteria for diagnosis and it is less difficult to diagnose asthma in this age group than in the younger children (NHLBI, 2007:281).

The National Asthma Education and Prevention Program’s NHLBI (2007:40) recommends that a thorough patient history be taken as well as the symptoms, physical examination and an assessment of the patient’s quality of life, to make a correct diagnosis of asthma. The report also suggests that a therapeutic trial with certain medications may aid the process of diagnosing a child with asthma. This strongly resembles the bronchodilator test in which the patient inhales a short-acting quick-relief bronchodilator.

It is often difficult to make an absolute diagnosis of asthma in children, that is why BTS/SIGN (2003:i7) developed an algorithm to assist in obtaining the diagnosis of asthma in children (refer to figure 2.1).

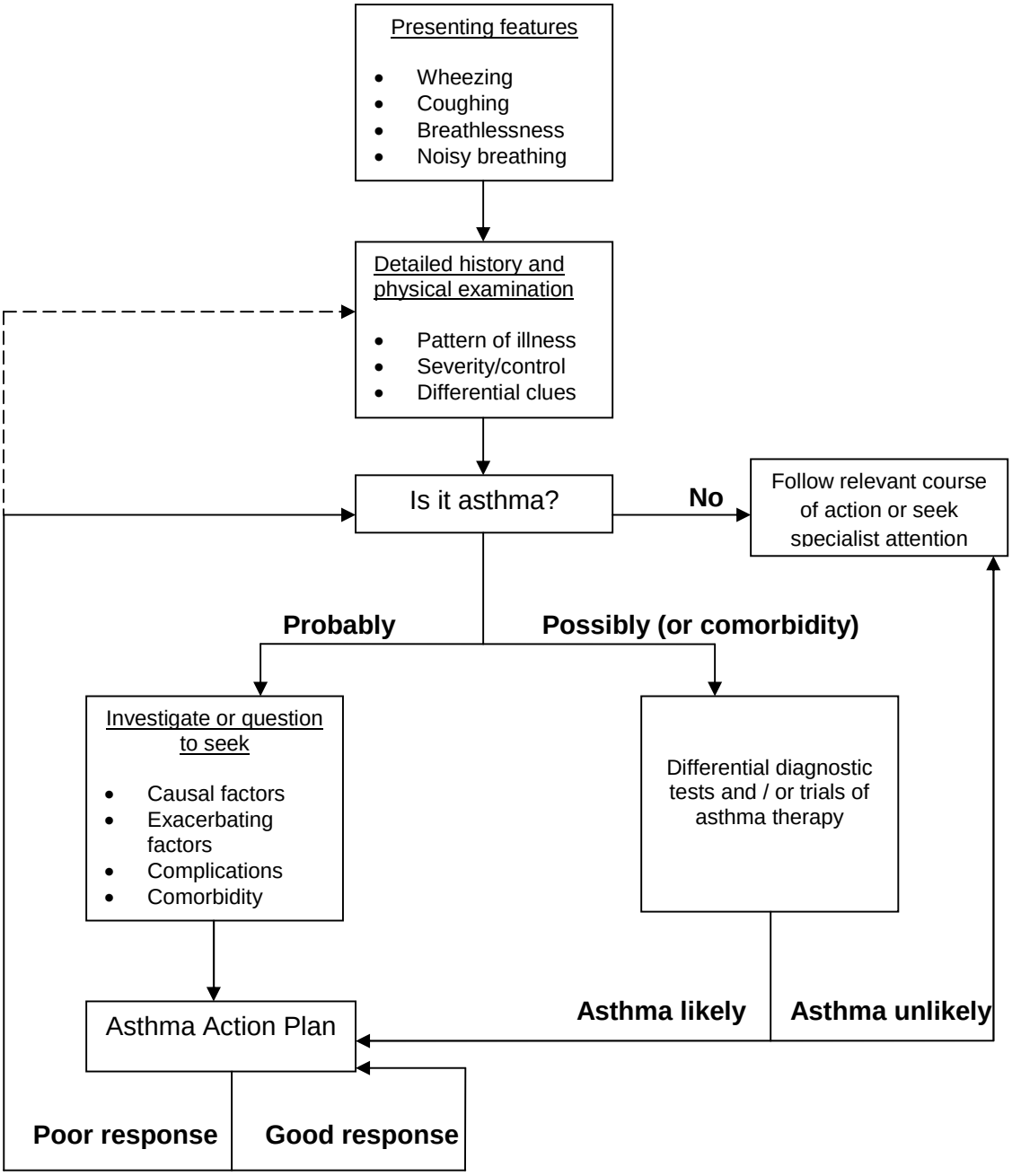


Figure 2.1: Algorithm for the diagnosis of asthma in children (Adapted from BTS/SIGN, 2003:i7).

2.3.3 Differential diagnosis

There are a number of diseases that may be mistaken for asthma (Löwhagen, 1999:852). In young children it is important to exclude any congenital abnormalities when making a diagnosis. Certain differential diagnoses are associated with a patient's age. In infants and children the most common differential diagnoses are (NHLBI, 2007:46; Boguniewicz *et al*., 2009:1020; Motala *et al*., 2009:899):

Obstructions involving large airways:

- Aspiration of a foreign body
- Vocal cord dysfunction
- Vascular rings
- Laryngotracheomalacia
- Airway stenosis
- Tuberculosis or enlarged lymph nodes

Obstructions involving small airways:

- Obliterative bronchiolitis
- Viral bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Cardiovascular disease

Other causes:

- Mediastinal mass
- Aspiration
- Primary immunodefiency
- Parasitic disease
- Hyperventilation syndrome and panic attacks
- GORD

Rosenthal (2002:148) suggests that differential diagnoses in younger children have to be considered with awareness. If a child presents with symptoms before six months of age, it is more likely to be an alternative diagnosis to asthma. A chronic cough does not necessarily mean that a child has asthma. In fact in most cases of chronic, productive coughs in children where wheezing is absent, a diagnosis of asthma should not be made. Further, if asthma-like symptoms have a sudden onset, it is more likely due to aspiration of a foreign body, for the reason that asthma symptoms usually appear gradually. Asthma frequently presents with

nocturnal symptoms. If the patient does not experience symptoms at night-time a diagnosis of vocal cord dysfunction can rather be made. When a patient does not respond to treatments, he or she should be evaluated again (Rosenthal, 2002:148).

2.4 Treatment guidelines of asthma

The NHLBI (2007:305) guidelines for the diagnosis and management of asthma, suggests that a stepwise approach should be followed when treating asthma in children and adults. The stepwise approach assists the clinician in deciding what the best treatment for a patient will be, but must only be used to help identify the individual patient's needs and not replace the process of decision making on the clinician's part. The stepwise approach for treating asthma in children 0 to 4 years can be seen in Table 2.2.

Table 2.2: The stepwise approach for managing asthma in children 0 - 4 years of age (Adapted from NHLBI, 2007:305,307).

Classify severity of asthma: Signs before treatment or adequate control			**Medication required to maintain long-term control**
	Symptoms Per day	**Night-time awakenings**	**Daily medications**
Step 1: Mild intermittent	≤2 days/week	≤2 nights/month	Preferred: • No daily medication • Short-acting β_2-agonist when needed.
Step 2: Mild persistent	>2/week but <1/day	>2 nights/month	Preferred: • Low dose inhaled corticosteroid Alternative: • Cromolyn • Leukotriene receptor antagonist
Step 3: Moderate persistent	Daily	>1 night/week	Preferred: • Low-dose inhaled corticosteroid and long-acting β_2-agonist • Medium-dose inhaled corticosteroids Alternative: • Low-dose inhaled corticosteroid and leukotriene receptor antagonist or theophylline If the patient experiences recurring severe exacerbations: Preferred: • Medium-dose inhaled corticosteroid

			Alternative: • Medium-dose inhaled corticosteroid and leukotriene receptor antagonist or theophylline
Step 4: Severe persistent	Throughout the day	>1/week	Preferred: • High-dose inhaled corticosteroids • Long-acting inhaled β_2-agonist • Corticosteroid tablets or syrup long-term Attempt to maintain control with high-dose inhaled corticosteroids and reduce systemic corticosteroids.

All patients, regardless of the severity of their asthma, must receive bronchodilator therapy as needed to treat symptoms. The severity of the exacerbation will determine how often this treatment should be used. Preferably the patient should receive an inhaled short-acting β_2-agonist. A face mask and space-holding chamber or a nebuliser, could especially help in small children (Department of Health, 2008:269). Alternatively they could also use an oral β_2-agonist. Daily use of a short-acting β-agonist, indicates that there is a problem with the control of the child's asthma and that long-term control therapy should be increased or initiated (NHLBI, 2007:305). If a child with asthma contracts a viral respiratory infection, it is advisable to increase bronchodilator therapy to four to six hourly for up to 24 hours and to consider systemic corticosteroids if the patient has a history of severe exacerbations. This treatment should only be implemented once every six weeks. Treatment should be reviewed every three months.

Currently few studies (Baker *et al*., 1999:414; Kemp *et al*., 1999:231) have been done on children younger than three years of age and the NHLBI (2007:291) suggested this treatment approach based on studies done on older children and adults, and extrapolating the results to suit younger children.

The stepwise approach for treating asthma in children between five and eleven years of age can be seen in Table 2.3 (NHLBI, 2007:306,308). Severity is still classified into four steps. Forced expiratory volume in one second (FEV_1) and peak expiratory flow rate (PEFR) is also taken into account in older children, because older children are able to give a reading.

Table 2.3: The stepwise approach for managing asthma in children 5-11 years of age (Adapted from: NHLBI, 2007:306,308).

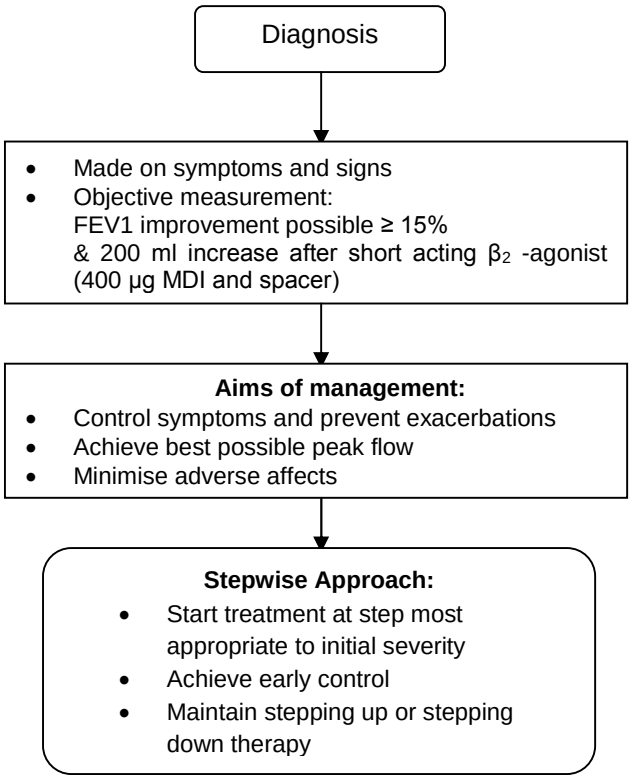
Classify severity of asthma: Signs before treatment or adequate control				**Medication required to maintain long-term control**
	Symptoms **Per day**	**Night-time** **awakenings**	**PEFR or FEV_1 variability**	**Daily medications**
Step 1: Mild intermittent	≤2 days/week	≤2 nights/month	≥ 80% per day < 20% at night	Preferred: • No daily medication • Short-acting β-agonist when needed. • If severe exacerbations occur, systemic corticosteroids are recommended.
Step 2: Mild persistent	>2/week but <1/day	>2 nights/month	≥ 80% per day 20-30% at night	Preferred: • Low dose inhaled corticosteroid Alternative: • Cromolyn • Leukotriene receptor antagonist • Nedocromil • Sustained release theophylline
Step 3: Moderate persistent	Daily	>1 night/week	>60 %-< 80% per day >30% at night	Preferred: • Low-dose inhaled corticosteroid and long-acting inhaled β-agonist • Medium-dose inhaled corticosteroids Alternative: • Low-dose inhaled corticosteroid and leukotriene receptor antagonist or theophylline If the patient experiences recurring severe exacerbations: Preferred: • Medium-dose inhaled corticosteroid and long-acting β-agonist Alternative: • Medium-dose inhaled corticosteroid and leukotriene receptor antagonist or theophylline

Step 4: Severe persistent	Throughout the day	>1/week Frequent	≤ 60% per day > 30% at nigt	Preferred: • High-dose inhaled corticosteroids • Long-acting inhaled β_2-agonist • Corticosteroid tablets or syrup long-term Attempt to maintain control with high-dose inhaled corticosteroids and reduce systemic corticosteroids.

For older children bronchodilator treatment can also be administered in case of an exacerbation or attack. The dosage is higher though, as the patient is allowed to take two to four puffs for up to three treatments at 20 minute intervals. One nebuliser treatment may also be sufficient. A course of systemic corticosteroids may be needed as well.

A step-up should be considered if control cannot be maintained with the therapy that is already being used. Before a step-up is done, first check the patient's adherence, inhaler technique, environmental control and the comorbid circumstances. A step-down can be made gradually, if the patient's asthma had been well-controlled over the past three months. The goal of the stepwise approach is to gain control as fast as possible, even using systemic corticosteroids, and then to assess the patient and step-down to the least medication required to maintain control (NHLBI, 2007:305). The NHLBI (2007:306) recommends stepping up one step if the patient's asthma is not controlled, but in older children, even two steps can be stepped up. The patient must then be re-evaluated within two to six weeks after using the treatment.

From the South African perspective, the treatment guidelines do not differ tremendously. This algorithm is, however, not necessarily clinically applicable to the treatment of children. Figure 2.2 shows the treatment guidelines of asthma (South Africa, 2003:55-56).



CLASSIFICATION OF SEVERITY OF ASTHMA

Classify severity at presentation

	Intermittent	**Persistent**		
		Mild	**Moderate**	**Severe**
Category	I	II	III	IV
Daytime symptoms	≤ 2/week	2-4 /week	> 4/week	Continuous
Night-time symptoms	≤ 1/month	2-4 /month	> 4/week	Frequent
PEFR (predicted)	≥ 80%	≥ 80%	60-80%	< 60%
START TREATMENT AT MOST APPROPRIATE STEP				

Step 1: Mild Intermittent Asthma

- Inhaled short acting β_2 agonist as required

Step 2: Mild Persistent Asthma

- Reliever: β_2 agonist as required
- Preventer: Add inhaled corticosteroid 400-800µg daily (Equivalent to beclomethasone MDI and spacer)

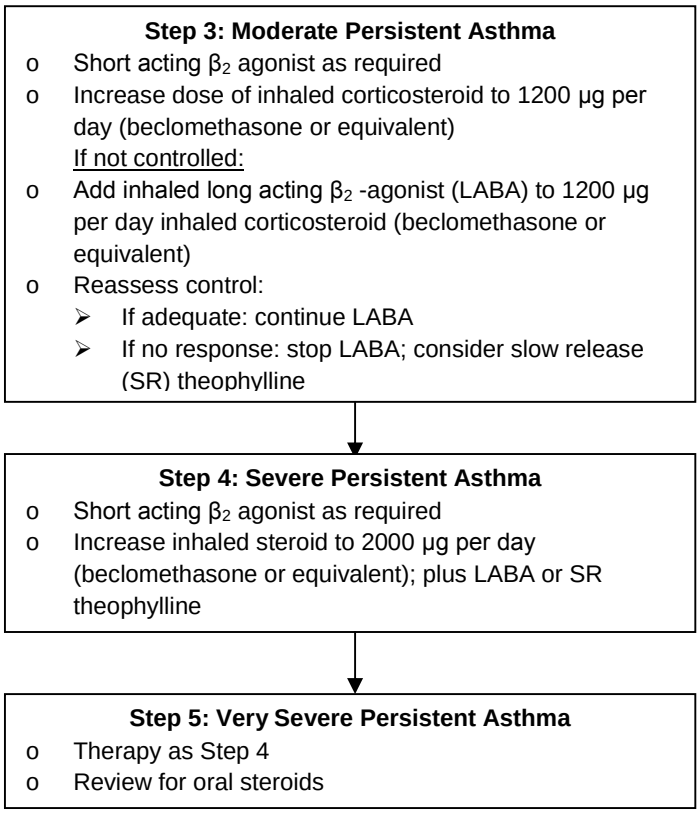


Figure 2.2: Algorithm for the treatment guidelines for asthma (Adapted from: South Africa, 2003:55-56).

2.5 Treatment of asthma

Asthma medications are classified into two main groups (AAAAI, 2007; Department of Health, 2008:271; Lalloo *et al*., 2007:19; Snyman, 2009a:14a):

- Bronchodilators
- Anti-asthmatics

The bronchodilators help with quick relief in case of an exacerbation or attack. Drugs in this group include sympathomimetic agents, methylxanthines and anticholinergic agents. They are also known as “relievers”.

The anti-asthmatics are also known as “controllers” or “preventers”. These drugs are taken daily to control persistent asthma, prevent attacks and to reduce airway inflammation. Drugs in these groups are the corticosteroids, leukotriene receptor antagonists and chromones (Snyman, 2009a:14a). Drugs for the treatment of asthma available in South Africa can be seen in Table 2.4.

Table 2.4: Classification of drugs used in the treatment of asthma in South Africa (Adapted from: Lalloo *et al*., 2007:21)

Controllers		**Relievers**
Anti-inflammatory action to prevent asthma attacks	**Sustained bronchodilator action but weak or unproved anti-inflammatory effect**	**Quick relief of symptoms and use in acute attacks as PRN dosage only**
Inhaled corticosteroids Beclomethasone Budesonide Fluticasone Ciclesonide	Long-acting beta-agonists Salmeterol Formoterol	Short-acting beta-agonists Salbutamol Fenoterol Terbutaline
Leukotriene modifiers Montelukast Zafirlukast Oral corticosteroids Prednisone Prednisolone Methylpredinisolone Methylprednisone	Sustained release theophylline preparations	Anti-cholinergics Ipratropium bromide

2.5.1 Bronchodilators

The process of bronchodilation is described in Figure 2.3 (Boushey, 2009:343). Cyclic adenosine 3',5'-monophosphate (cAMP) promotes bronchodilation (Ward *et al*., 1995:534). Sympathomimetic drugs, such as beta-agonists increase the intracellular levels of cAMP through increasing the rate of adenyl cyclase (AC) synthesis. Methylxanthines, like theophylline inhibit phosphodiesterase (PDE), which slows the degradation of cAMP. Anticholinergic drugs and theophylline also inhibit bronchoconstriction.

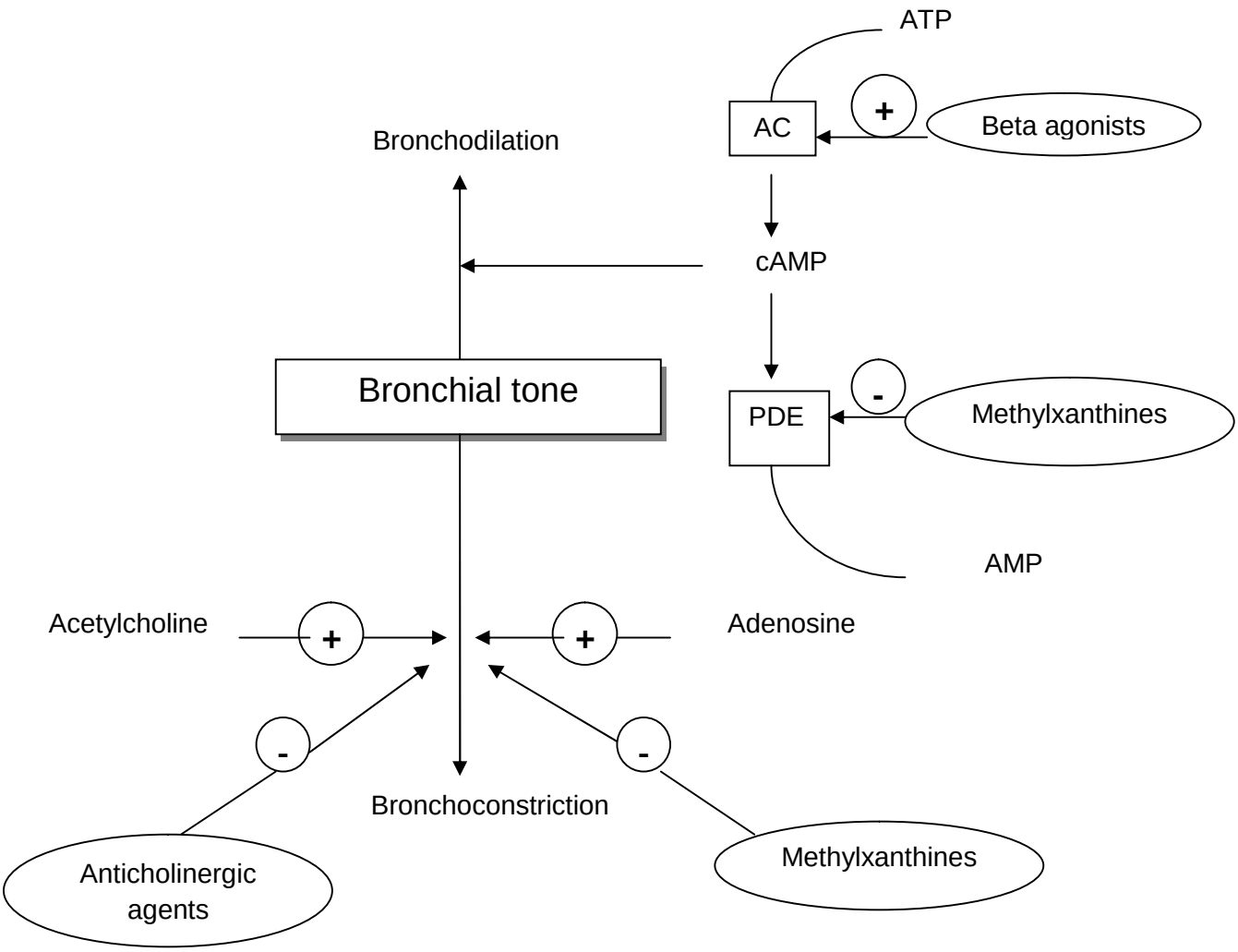


Figure 2.3: Bronchodilators and their effects on the bronchial tone (Adapted from Boushey, 2009:343).

2.5.1.1 Sympathomimetic agents

The mechanism of action of sympathomimetic agents in asthma lies in the fact that they relax the smooth muscle of the airways that lead to bronchodilation (Sears & Lötvall, 2004:152). This group also reduces the release of substances from mast cells that lead to bronchoconstriction (Figure 2.3) (Boushey, 2009:342). These agents are widely used in the treatment of symptoms of asthma and to bring on immediate relief in case of an attack. Adrenoreceptors are present on the smooth muscle of the airway and by stimulating the β_2-receptors with sympatomimetic agents, that mimic the effect of the sympathetic nervous system, the smooth muscle relaxes and bronchodilation can take place (Westfall & Westfall, 2006; Boushey, 2009:342).

Drugs in this category include adrenaline, ephedrine and isoproterenol, which are all non-selective sympathomimetic agents (Westfall & Westfall, 2006).

Adrenaline and ephedrine are used to induce quick bronchodilation, though their side-effects cause that they are not being prescribed regularly (Sears & Lötvall, 2004:152). Adrenaline's non-selectivity causes cardiac side-effects such as arrhythmias and ephedrine leads to central nervous system side-effects (Turpeinen *et al*., 1984:667; Haller & Benowitz, 2000:1833).

Isoproterenol is used more often and induces maximum bronchodilation within five minutes of inhalation (Boushey, 2009:344). High doses of inhaled isoproterenol may lead to cardiac arrhythmia that may cause death. Formoterol is unique in the sense that it can cause a long-lasting bronchodilative effect, but has a very fast onset of action, approximately one to three minutes after inhalation (Sears & Lötvall, 2004:152).

The drugs that are used most often in asthma therapy are β_2-selective agonists. Salbutamol, terbutaline and fenoterol are short-acting β_2-agonists (Lalloo *et al*., 2007:21). They are available as inhalation preparations or in some cases as syrup or in tablet form (Snyman, 2009a:166). These preparations can also be inhaled through a nebuliser. A nebuliser will be used in cases where the patient is unable to co-ordinate the metered dose inhaler inhalation. The short-acting β_2-agonists lead to bronchodilation within 30 minutes of taking the medication and the effects last up to four hours (Boushey, 2009:344). Terbutaline is available for subcutaneous injection. This dosage form is used in emergencies only, where the patient's inhalation therapy has been unsuccessful in opening the airways. It has a slightly longer duration of action, leading to accumulation of the drug in the patient's system if it is injected repeatedly (Westfall & Westfall, 2006).

Salmeterol and formoterol are more recent long-acting β_2-agonists (Vassiliou & Zipitis, 2006:382). They have high lipid solubility, which causes them to dissolve in the smooth muscle cell membranes of the airways or to attach to connecting molecules close to the adrenoreceptor (Boushey, 2009:344). This leads to an effect that lasts up to 12 hours and functions as a depot to distribute the drug to the neighbouring β-adrenoreceptors. Long-acting β_2-agonists can therefore be seen as a controller and should not be used as monotherapy in the treatment of asthma, but in combination with inhaled corticosteroids (Lalloo *et al*., 2007:24 & Boushey, 2009:344). The safety of long-acting β_2-agonists was questioned and products containing salmeterol or formoterol were issued with a warning label in the USA, because of a higher risk of asthma-related deaths and more frequent serious asthma exacerbations. (NHLBI, 2007:232; Nelson *et al*., 2006:26; Mann *et al*., 2003:70). These products are not allowed to be prescribed as monotherapy and must always be accompanied by an inhaled corticosteroid.

Although sympathomimetic drugs are available in different types of dosage forms, the inhalation route produces the best local effect for bronchodilation and the least systemic effects. When using aerosol treatment, it is important to remember that even when the particle size is most favourable (between 2 and 5µm), 80-90% of the particles are still deposited in the mouth and pharynx (Boushey, 2009:342). In a study done by Usmani *et al.* (2005:1503) it was found that larger particles of a β_2-agonist cause better bronchodilation than smaller particles. Inhalation therapy can, however, be improved by the accumulation of aerosol particles in the different parts of the airways, that have an affinity for them (Usmani *et al.*, 2005:1497). Patients also have trouble with the co-ordination of the inhaler and often do not use their inhalers correctly. Oral β_2-agonists are not recommended in asthma therapy, because of its slow onset of action and the side-effects that might occur more regularly than with inhalation devices. Their duration of action is extended and therefore might prove useful in patients with nocturnal asthma. Intravenous and injectable β_2-agonists are used in emergencies only and are usually very potent bronchodilators (Rossiter, 2010:536).

Adverse effects of β_2-agonists are rare and occur mostly if the drugs are absorbed systemically. Fine tremors, palpitations, dizziness and other cardiac side-effects may occur (Taketomo *et al*., 2000:856). High doses may lead to nausea and vomiting and prolonged use may cause reversible hypertrichosis (Rossiter, 2010:537). Hypersensitivity to β_2-agonists is not seen very often, but may cause bronchospasm, urticaria and angioedema. Also taking more than one β_2-agonist together is unsafe, because their potencies are unknown and could lead to an accumulated effect. β_2-agonists and sympathomimetic drugs are considered safe when administered in correct doses and is the first line of treatment in paediatric asthma (Rossiter, 2010:537; Boushey, 2009:344).

2.5.1.2 Anticholinergic drugs

Anticholinergic agents, also referred to as antimuscarinic agents, are of use in asthma through their inhibiting effect on acetylcholine (Bateman *et al*., 2009:533). As can be seen in figure 2.1, the anticholinergic drugs inhibit bronchoconstriction by competitively inhibiting the effect of acetylcholine at muscarinic receptors. This causes the airway smooth muscle to contract less and increases the secretion of mucus. Therefore, they are potent broncholdilators. Atropine, the model anticholinergic agent, leads to bronchodilation at a much lower dose than that needed to increase heart rate. Atropine can therefore be selective, to only act in the lungs. Inhalation preparations could increase the selectivity and the effect of atropine (Boushey, 2009:347).

An anticholinergic drug often used in asthma is ipratropium bromide. It is a selective quaternary derivative of atropine (Boushey, 2009:347). Relatively high doses of ipratropium can be administered to muscarinic receptors in the airways, because ipratropium is poorly

absorbed by the airways and does not have effects on the central nervous system (Restrepo, 2007:833). Ipratropium is particularly useful in patients who are intolerant of inhaled β-agonists and in infants under one year of age (Murphy, 2007:77). Antimuscarinic drugs are not as effective as β-agonists to initiate bronchodilation, but by adding ipratropium to a β-agonist, the bronchodilation effect of the bronchodilator may be improved (Boushey, 2009:347).

Adverse effects of ipratropium are very rare, because of its poor absorbance by the lungs. The patients may experience some anticholinergic effects, but it does not occur often. Patients with prostatic hypertrophy, narrow-angle glaucoma or bladder neck-obstruction should use these drugs with caution (Taketomo *et al*., 2001:527; Rossiter, 2010:540).

2.5.2 Anti-asthmatics

In order for asthma patients to have increased quality of life, drugs that control their asthma on a daily basis should be used. Anti-asthmatic drugs can be classified into groups that control asthma and drugs that prevent asthma. Preventers are the inhaled corticosteroids (glucocorticoids) and the controllers are the long-acting β_2-agonists and the leukotriene receptor antagonists (Rossiter, 2010:531).

2.5.2.1 Glucocorticoids

The glucocorticoids have been used to treat asthma for over 50 years (Barnes, 2006:S299). Their anti-inflammatory mechanism makes these drugs ideal to reduce asthma exacerbations. The most significant action of the glucocorticoids is the inhibition of the eosinophyllic airway mucosal inflammation in the airways. They also have the ability to potentiate the effects of β_2-agonists, which is why there are a number of combination products on the market (Boushey, 2009:347).

Glucocorticoids are available in different preparations. Oral and parenteral treatment are only given to patients that require emergency treatment and patients that experience a deterioration of their asthma control. This is because of the side-effects that are experienced when using systemic corticosteroids over a long period. For maintenance therapy of asthma inhaled corticosteroids are recommended (Barnes, 2006:S299).

Inhaled corticosteroids are designed to deliver the drug to the airways with minimum systemic absorption. Their high lipid-solubility helps with this function. Inhaled glucocorticoids come in different strengths and the patient's asthma severity will indicate the dose to be given. Compared to oral corticosteroids, inhaled corticosteroids have minimal chances of causing systemic toxicity when the patient is on continued therapy. In very high doses suppression of the adrenohypophyseal axis has been reported (Rossiter, 2010:538). However, fatalities have occurred when a patient was taken off systemic oral corticosteroids

and inhaled corticosteroid therapy was initiated. This is due to the adrenal suppression that followed (Boushey, 2009:348).

The main problem that could occur with topical inhaled corticosteroids is oropharyngeal candidiasis. To prevent this condition, patients are advised to gargle with water and rinse the mouth after every inhalation or to use a spacer (Boushey, 2009:348; Rossiter, 2010:539). The patient may experience hoarseness as well, because of the direct effect the inhaled steroids have on the vocal cords. If a patient uses inhaled corticosteroids over a long period of time, it could lead to an increased risk of osteoporosis and cataracts in adults and an impaired growth rate in children. A very rare disease, Churg Strauss syndrome, may occur when a sudden reduction in systemic corticosteroid therapy is experienced (Lilly *et al*., 2002:S2). This syndrome is categorised as small vessel vasculitis that is associated with eosinophilia and occurs in patients with asthma and sinusitis (Lilly *et al*., 2002:S2).

Products used for inhalation therapy of corticosteroids in South Africa are budesonide, beclomethasone, fluticasone and ciclesonide (Lalloo *et al*., 2007:24). Budesonide and beclomethasone appear on the Essential Medicines List of South Africa (Department of Health, 2008:269). Beclomethasone, budesonide and fluticasone are proved to have the same effectiveness if they are given in the same doses (Rossiter, 2010:538). Fluticasone, however, is more likely to cause adrenal suppression. The important distinction that can be made between relievers and controllers is that patients have to continue their controller therapy even after the symptoms of asthma have disappeared. Patients start out with an oral corticosteroid, such as prednisone. The dose is then gradually lowered until airway obstruction has improved. If the patient had been on chronic oral therapy, it is advisable to give a high-dose inhalation corticosteroid to wean the patient from the chronic steroids. After that, the patient should receive the lowest dose inhalation corticosteroid possible, to still maintain control of the asthma. The inhaled corticosteroids are not curative, but remain the most effective way to control asthma symptoms and minimise hospitalisation (Boushey, 2009:348).

Fortunately, the prescribing patterns of inhaled corticosteroids have changed over the last few years. In a study done by Van Staa *et al*. (2003:584), it became apparent that the use of inhaled corticosteroids has doubled in some European countries within a period of seven years. This is important, because inhaled corticosteroids are considered to be the best way to control asthma. In the same study it was seen that the use of oral corticosteroids and bronchodilators have decreased, which means that patients with asthma are better controlled than before and experience fewer acute attacks (Van Staa *et al*., 2003:584).

2.5.2.2 Methylxanthine drugs

In figure 2.3 it can be seen that methylxanthines have an effect on the bronchial tonus process, by inhibiting bronchoconstriction and PDE and leading to bronchodilation (Boushey, 2009:345). These mechanisms of action make the methylxanthines ideal for the treatment of asthma. Theophylline, theobromine and caffeine are the important methylxanthines (Scheindlin, 2007:236). Of these three theophylline and a theophylline-ethyldiamine complex, aminophylline, are most commonly used to treat asthma. With the development of the anti-inflammatory agents for the chronic treatment of asthma and β_2-agonists for use in acute asthma attacks, theophylline has been phased out, because of its systemic side-effects. It is, however, to the patient's economical advantage, especially in communities with limited health care resources (Boushey, 2009:345; Barnes, 2003:813).

Theophylline blood levels should be taken regularly if a patient is on solitary maintenance treatment or in combination with an inhaled corticosteroid or if a patient is using potentially interacting medications (Rossiter, 2010:542). It has a narrow therapeutic window and its therapeutic and toxic effects depend on plasma concentrations of theophylline (Weinberger & Hendeles, 1996:1382). A range of 5-20mg/L is associated with an improvement in pulmonary function. From plasma concentrations of 15mg/L adverse effects begin to occur (Boushey, 2009:346). Theophylline has significant side-effects that could decrease patient adherence. It has an effect on the central nervous system by causing nervousness and insomnia, as well as medullary stimulation and convulsions, which could be fatal. Cardiovascular effects can also be experienced as sinus tachycardia and an increase in cardiac output at plasma levels of 25-35mg/L. Arrhythmias and seizures occur at plasma levels higher than 35mg/L and could be fatal. General adverse effects include gastro-intestinal symptoms, such as reflux, diarrhea, nausea, vomiting, abdominal pain, dizziness, muscle cramps and tremors. The adverse effect does not necessarily occur according to the serum levels. Arrhythmias and convulsions can occur without observing the other side-effects (Taketomo *et al*. 2001:910; Riordan *et al*., 2002:400).

The clearance rates of theophylline may vary. It is metabolised in the liver by hepatic enzymes (Hendeles *et al*., 1985:104S). Patients with liver disease may experience toxicity even when normal doses are taken. Cigarette smoke as well as certain changes in diet causes induction of hepatic enzymes and this could lead to a faster clearance rate and consequently sub-therapeutic doses. Food may also cause a sudden release of the drug, which could potentially lead to toxicity (Murphy, 2007:205). In normal adults the clearance rate is approximately 0.69mL/kg/min, but in children clearance rates are much faster at values between 1 and 1.5mL/kg/min. Neonates and young infants have the slowest clearance, therefore theophylline is not given to very young children often (Boushey, 2009:346).

Theophylline is available as oral sustained release or immediate release preparations or parenteral intra-venous infusion bags as aminophylline that is administered over a period of 30 minutes. IV aminophylline should only be given to children that are in the intensive care unit, where they can be monitored with an ECG, because children are especially prone to develop some of the adverse effects of theophylline. Syrups containing theophylline may also cause adverse effects in children, due to the significant amount of alcohol in these preparations (Murphy, 2007:214). Duplication of methylxanthines can be very dangerous and is mostly used as second line therapy, because of their pharmacokinetic unpredictability. If the patient is on long-term use of theophylline, it is advisable to use sustained release preparations that cause less variation in plasma concentrations (Rossiter, 2010:542).

2.5.2.3 Leukotriene pathway antagonists

Leukotrienes are involved in the inflammatory process. Therefore, with the inflammation caused by asthma, leukotrienes are being released, causing bronchoconstriction, increased bronchial reactivity, mucosal oedema and the hyper secretion of mucus (Boushey, 2009:349).

There are two approaches by which the leukotriene pathway can be inhibited to reduce inflammation and cause bronchodilatation. Firstly 5-lipoxygenase, the enzyme necessary for leukotriene synthesis, can be inhibited and secondly by blocking the binding of leukotriene D_4 to its receptor on the target tissue. There are drugs available in both categories. Zileuton is a 5-lipoxygenase inhibitor. It is, however, not prescribed often and not available in South Africa, because it could cause liver toxicity and requires a four times daily dosing. Montelukast and zafirlukast are leukotriene receptor antagonists. Their effects on airway inflammation are not quite as noticeable as found with inhaled corticosteroids, but they are equally effective in reducing the occurrence of asthma exacerbations. The main benefit of these drugs is that they are taken orally (Boushey, 2009:350). This is a more convenient dosage form to most patients, as they are not compliant with inhalation devices. Especially children show poor compliance with inhalation devices. Therefore, montelukast can be beneficial to children and can be prescribed to children as young as two years of age (Boushey, 2009:349 & Rossiter, 2010:543).

Leukotriene receptor inhibitors are especially effective in reducing aspirin-induced asthma (Dahlen *et al*., 2002:9). This type of asthma occurs in some asthma patients due to the inhibition of cyclooxygenase by aspirin. Figure 2.4 shows the pathways that arachidonic acid follows in the inflammatory process (Celotti & Durand, 2003:150). It can either follow the cyclooxygenase (COX) pathway or the 5-lipoxygenase (LOX) pathway. When a patient takes aspirin, it will inhibit the COX pathway, because it is a non-selective COX-inhibitor. This will force arachidonic acid to follow the LOX pathway, causing leukotrienes to form and leading

to bronchoconstriction. At this point leukotriene pathway modifiers will be able to prevent asthma. This reaction can also be brought on by any non-steroidal anti-inflammatory drugs (NSAIDs) (Celloti & Durand, 2003:150; Szczeklik *et al*., 2000:432).

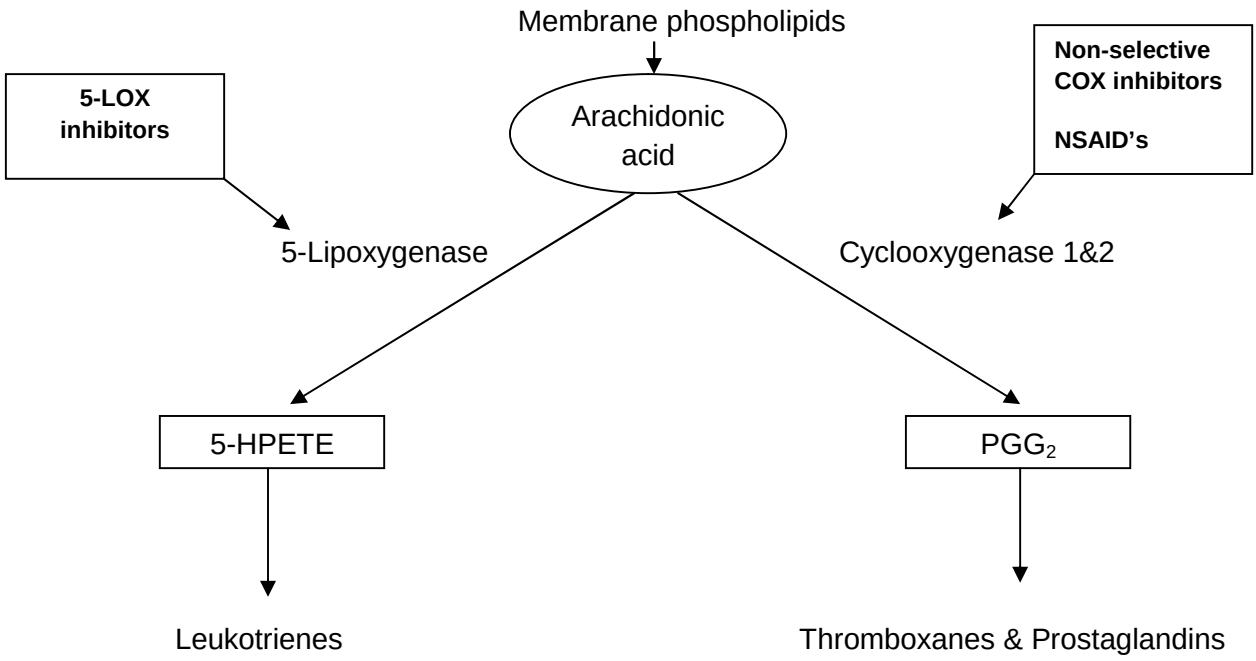


Figure 2.4: Arachidonic acid metabolism and inhibitors (Adapted from: Celotti & Durand, 2003:150).

Leukotriene receptor inhibitors do not have many adverse effects (Rossiter, 2010:544). Montelukast can lead to some gastrointestinal effects, such as diarrhoea, nausea and dyspepsia. It can cause some dizziness and fever, along with headaches and a rash. Zafirlukast, in addition, can lead to severe hepatic impairment, and is a cytochrome P450 inhibitor which could cause interactions with drugs that are metabolised by the CYP 3A4 and CYP 2C9 isoenzymes, such as warfarin, erythromycin, phenytoin and carbamazepine (Murphy, 2007:224). Theophylline also has an interaction with zafirlukast, in which zafirlukast levels are reduced to subtherapeutic concentrations. A very important side-effect that could occur with leukotriene receptor inhibitors is that of Churg-Strauss syndrome (Murphy, 2007:222). With the use of leukotriene modifiers and high dose corticosteroids to control the symptoms of asthma, the use of systemic corticosteroids have been decreased or avoided completely (Lilly *et al*., 2002:S6). This reduction in systemic corticosteroid use is one of the clinical risk factors of Churg Strauss syndrome. The use of leukotriene receptor antagonists therefore, does not cause Churg Strauss syndrome, but their effects on asthma control, leads to a reduction of the use of corticosteroids, which could cause Churg Strauss syndrome. Churg Strauss syndrome rarely occurs in paediatric patients. Cases of the

disease that have been reported in younger patients, occurred in older children and adolescents (Lilly *et al*., 2002:S6).

2.5.3 Other drugs used to control asthma

Cromolyn and nedocromil

Cromolyn, also known as disodium cromoglycate, and nedocromil are used to prevent asthma due to seasonal allergies or exercise (Bjermer, 2001:711). They have an anti-allergic mechanism of action, by inhibiting inflammation in response to inhalation of an allergen. They have a specific action, by inhibiting mast cell degranulation in lung tissue but not in skin. It can be taken shortly before exercise as an acute protective measure, to block bronchoconstriction or it can be used prohylactically to reduce the use of symptomatic relievers. Cromolyn and nedocromil are only available in aerosol form, as metered-dose inhalers, microfine powders or aerolised solutions. This is due to their extreme insolubility and low bioavailability. They can be considered as a substitute for inhaled glucocorticoids; however, cromolyn has to be taken four times daily, which could prove inconvenient to the patient. Cromolyn was used extensively in children, especially in children at the ages where rapid growth occurred, but has been phased out (Boushey, 2009:349). Cromolyn (cromoglicic acid) usage has been discontinued in South Africa (Rossiter, 2010:528). The effectiveness of cromolyn therapy compared to inhaled corticosteroid and other asthma maintenance therapies in children cannot be proved, but it is concluded that cromoglicic acid will not be reinstated as asthma therapy in South Africa (Van der Wouden *et al*., 2008:2; WHO, 2009b:57).

Ketotifen

Ketotifen is an anti-histamine that can be used to prevent asthma. It is relatively selective for H_1-receptors and produces an effect by stabilising the mast cells and inhibiting the release of mediators from cells that are responsible for allergic reactions. It has been approved for use in children older than 6 months in the case of mild, atopic asthma. In children younger than three years who suffer from atopic eczema or hay fever, it may be useful in combination with a bronchodilator. It is available in tablets, slow-release tablets, drops and syrup. The oral form of ketotifen makes it more convenient for patients, especially children, who have trouble using an inhaler. This makes ketotifen a popular choice of asthma prevention. It should, however, be noted that ketotifen should not be used to treat acute asthma attacks (Rossiter, 2010:544; Boulet *et al*., 1999:S8).

2.5.4 Combinations of asthma drugs

In cases where the patient's asthma is insufficiently controlled with an inhaled corticosteroid, a combination of a long-acting inhaled β-agonist and an inhaled corticosteroid can be used.

This treatment is more useful than doubling-up the dose of the inhaled corticosteroid alone (Boushey, 2009:352). Long-acting β-agonists cause bronchodilation, but in combination they also improve the local effects that an inhaled corticosteroid has on the airways. Therefore it was beneficial for researchers to develop preparations that include both of these drugs. The preparations that are available in South Africa are either fluticasone and salmeterol or budesonide and formoterol (Rossiter, 2010:439; Motala *et al*., 2009:905). Combining an inhaled corticosteroid with a long-acting bronchodilator is not only more effective for the patient's asthma control, but it is cost-effective as well (Andersson *et al*., 2001:505). It is also easier for a patient to carry one inhaler instead of two or three. This facilitates patient compliance, which is an important factor in the control of asthma.

Other combinations that are available to patients are those that contain two bronchodilators such as ipratropium and salbutamol or fenoterol. They can only be used in acute attacks and would provide the patient with fast-acting and potent bronchodilation (Rossiter, 2010:541).

2.5.5 The future of asthma therapy

Anti-IgE drugs

A new class of drug called anti-immunoglobulin E (IgE) has been developed to assist in the treatment of asthma. Omalizumab is the first drug in this class and has after many years of research been approved by the Food and Drug Administration (FDA) in the USA (FDA, 2009). The negative aspects of this drug are that only certain patients may benefit from it and it is not widely available. The cost and administration of omalizumab will be a problem to patients (Cook, 2004:14). It has to be administered by a specialist or clinicians who are prepared to treat anaphylaxis if it should occur. It is not available in South Africa. Its mechanism of action works on the principle of inhibiting the inflammatory process by blocking IgE, which usually binds to mast cells and sets off the inflammatory process, after a patient has come into contact with an allergen. Patients with allergy related asthma might benefit from omalizumab over a period of approximately three months. In studies done on patients, the plasma IgE levels were barely discernible after ten weeks and bronchospasms had decreased considerably (Cook, 2004:14).

Purmactant

This drug is not available yet but shows great promise in preventing asthma. It is manufactured as a powder and delivered to the lungs by inhalation. It coats the lungs and acts like a surfactant that is naturally found in the body. This works like a lining in the lungs and helps to protect the lungs from allergens and irritants. In studies done the patients received purmactant 8 hours and 30 minutes before exposure to an allergen. The immediate asthmatic response, which usually occurs within 15 minutes of exposure, was eliminated and

the late asthmatic response (3 to 10 hours later) showed signs of improvement (Cook, 2004:14).

Other

Some medications that may be considered as helpful to patients with asthma have no proven benefits. This is especially true in childhood asthma. Antibiotics, cough mixtures and mucolytics and antihistamines have proved useful for other allergy-related diseases, but not in asthma. In a study done in France on the dispensing of antibiotics, antitussives and mucolytics to asthma patients, it was found that these medications were dispensed especially during asthma exacerbations (Laforest *et al.*, 2008:58). It was observed that 63.2% of asthma patients received antibiotics, 55.8% received mucolytics and 27.2% received antitussives, although there is no proof that the patients benefit from these added therapies. Dispensing patterns of antibiotics were seen to be inversely related to asthma control patterns. In other words, the more uncontrolled the patients' asthma was, the more antibiotics they received. This study suggested that education programmes should be implemented to ensure the uniformity of dispensing patterns and treatment guidelines (Laforest *et al.*, 2008:62). Complementary and alternative medicines have not been researched enough to show clear uses and recommendations in asthma therapy (Motala *et al*., 2009:906; NHLBI, 2007:240).

2.6 The prevalence of asthma

2.6.1 General

The WHO calculated that approximately 300 million people globally suffer from asthma (WHO, 2008). The problem is that it is still under-diagnosed and under-treated in developing countries as well as in first world countries. The most asthma-associated deaths, however, occur in countries with a lower income. According to a study done by Bradshaw *et al.* (2007), asthma is eighth on the list of causes of disease burden in South Africa. The only other chronic disease that creates a greater burden is HIV/AIDS.

2.6.2 South Africa

In South Africa the situation with asthma and especially childhood asthma, seems not to be under control. South Africa's asthma prevalence is ranked 25th globally with 8.1% of the population presenting with asthma symptoms (Masoli *et al.,* 2004:9). The results from a study done by Zar *et al*. (2007:563), shows that there was a consistent rise in the prevalence of asthma among young adolescents. This study was performed over a seven-year period and was able to indicate a significant change in the prevalence of asthma over a relatively short period of time. There can be many reasons for the increase in prevalence. Africa has some risk factors that are not as common in the rest of the world (Wjst & Boayke, 2007:e72). Local

plant life and certain types of grass, animal dander, grass mats and mud are only some of the causes of asthma in Africa. Southern Africa has a higher prevalence of asthma than the rest of Africa (Masoli *et al*., 2004:115). In South Africa specifically the risk of asthma due to occupational hazards from the mines is increasing as well (Wjst & Boakye, 2007:e72). South Africa also has a problem in terms of the mortality rate associated with asthma (Masoli *et al*., 2004:10). In the Global Burden of Asthma report for GINA (Masoli *et al.*, 2004:10) South Africa was ranked fourth in asthma mortality in the age group 5 to 34 years of age. The fatality rate of asthma in South Africa was ranked fifth, with 18.5 deaths per 100 000 asthmatics. This indicates that there is definitely a problem regarding patients' control over their asthma. After pneumonia and gastroenteritis, asthma is the third leading cause for hospitalisations in South Africa, especially in children (Masoli *et al*., 2004:115).

2.6.3 Children

Asthma is currently the most common chronic disease in children (WHO, 2008). In the United States an estimated 7.1 million children under the age of 18 years suffer from asthma and 4.1 million of them experienced an asthma attack in 2009 (American Lung Association, 2010). In South Africa it affects 10-20% of children (Zar *et al.*, 2007:560). In studies done in South Africa the prevalence of asthma has increased from 1995 to 2002 in adolescents and it is still increasing in children in sub-Saharan Africa (Pearce, 2007:758; Zar *et al.*, 2007:565). Furthermore, it has been found in the United States that the prevalence of asthma is higher in black children than in white children in an urban setting. That does not necessarily mean that black children are more prone to asthma. It depends on the environment and the neighbourhood a child lives in (Gupta *et al*., 2008:644). In South Africa asthma seems to have a higher prevalence rate among people of mixed race, followed by black and then white people (Masoli *et al*., 2004:116). Tobacco smoke also has an effect on the degree of exposure a child experiences to pollutants. In many cases where the caregiver is a smoker, a child with asthma will suffer more attacks. Children with asthma in low-income families are being more exposed to tobacco smoke from their caregivers. Therefore, by containing and aiming to reduce caregiver smoking, asthma morbidity in school-age children might be reduced (Kumar, *et al*., 2008:758).

In a study done in the USA by Litonjua *et al*. (1998:181) it was found that asthma in children is more likely to occur in patients whose parents also suffer from the condition. Other allergic conditions are often associated with asthma, but it is to be expected that children will develop the atopic condition similar to that of their parents (Litonjua *et al*., 1998:181; Alford *et al*, 2004:1046).This study showed that inheritance from the child's mother is more probable.

2.6.4 Geographical prevalence

The neighbourhood in which a patient lives can be a contributing factor to whether or not a patient develops asthma. In a study done by O'Connor *et al.* (2008:1134), it was found that cities in the United States polluted the air with NO_2, SO_2 and particulate matter with an aerodynamic diameter of less than 2.5µm (PM2.5). The concentration of these agents was taken near the homes of the study population. Children between the ages of 5 and 12 years that live in urban neighbourhoods and who were suffering from asthma were included. The results showed that there are links between the exposure to pollutants and overall respiratory health in children. In areas with higher concentrations of NO_2, SO_2 and PM2.5, children experienced a decrease in respiratory function. Higher NO_2 concentrations caused patients to experience asthma symptoms more frequently (O'Connor *et al*., 2008:1135). According to Edwards (2004:60) a preventative plan should be implemented to limit exposure to environmental triggers. These triggers, such as pollutants in the air from motor vehicles, types of building materials used in construction and poorly ventilated areas, are all results of urbanisation and should be identified, controlled and eliminated in order to control asthma in urban areas. Urbanisation plays a role in how asthma prevalence will change in the future. It has been predicted that the world's urbanised population will increase from 45% to 59% by 2025 (Masoli *et al*., 2004:1). With that increase, more people will be exposed to pollutants, therefore it is estimated that the prevalence of asthma will increase to approximately 400 million people globally (Masoli *et al*., 2004:1).

2.6.5 Gender prevalence

In general, studies have shown that the female sex is a risk factor for developing asthma (Wjst & Boakye, 2007:203). In children, however, that is not the case. Before puberty the prevalence of asthma is much higher in boys than in girls. It is likely that hormonal changes are the cause of the reverse in prevalence after puberty in males and females (Postma, 2007:S133, S141).

2.6.6 Treatment by a general practitioner or specialist

The treatment of asthma can sometimes be more complicated. The help of a specialist is then brought in. Patients can be referred to a pulmonologist, that focuses specifically on lungs, an allergist that is concerned with allergies and may have a link to asthma, because of the high prevalence of allergies among asthmatic patients or for child-specific cases a paediatrician. It is also possible for patients to be referred to a paediatric pulmonologist (Alford, 2003:21). In a study done by Zeiger *et al* (1991:1160), it has been proved that a patient's outcome after an emergency room visit due to an asthma attack was better when that patient was referred to a specialist. The patient's outcome was less satisfactory when a general practitioner was involved in the care after the attack. A patient will usually be referred

to a specialist in allergies or pulmonology in the following cases (NHLBI, 2007:68; Motala *et al*., 2009:909; BTS/SIGN, 2003:i7):

- When a patient experiences a severe asthma exacerbation.
- If the patient does not respond to therapy and does not seem to have the asthma under control after three to six months of therapy.
- If it is a difficult case to diagnose and other conditions complicate the diagnosis of asthma.
- If supplementary diagnostic tests are required, for example skin allergy testing, bronchoprovocation or a bronchoscope.
- When a patient is being considered for immunotherapy.
- If a patient has trouble with adherence and complications of the therapy and needs additional advice.
- If a patient requires step 4 care or higher. Step 3 for paediatric patients aged 0 to 4 years.
- If a patient experienced an exacerbation that requires hospitilisation or more than two bursts of oral corticosteroids in one year.
- If a patient has a history of occupational or environmental risks that may be provoking or contributing to asthma symptoms.

2.7 Patient adherence to asthma medication

Patient adherence makes up an important part of asthma therapy. It determines whether patients are using their medication correctly and treating it as a chronic disease that needs constant attention and treatment. Adherence can be defined as “the extent to which patients take their medications as prescribed by their health care providers” (Osterberg & Blaschke, 2005:487). There is a difference between the terms “adherence” and “compliance” and they are not similar as previously thought. Non-compliance has acquired a negative connotation as it is seen as a patient’s incompetence to take the medication as instructed by their health care professional or a patient’s deliberate attempt not to take the medication (Horne, 2006:66S). Compliance is also thought not to include the patient in the decision-making process when establishing a therapeutic plan and does not encourage an alliance between the patient and the health care provider (Osterberg & Blaschke, 2005:487). According to Bester and Hammann (2008:20), a patient can be considered adherent with medicine

treatment if the patient claimed for 10 or more refills in a period of 12 months. This means that 80% of the medication was used.

Non-adherence to medication can be classified into two groups (Horne, 2006:67S):

- Unintentional non-adherence
- Intentional non-adherence

Unintentional non-adherence is when the patient is not taking the medicine as prescribed due to factors beyond his/her control. This may be linked to the patient not being able to recall what was said during the consultation, the patient not understanding the health care provider due to language barriers or the patient being forgetful.

Intentional non-adherence occurs when the patient makes a decision not to use the medication or to use the medication in a different way than it had been prescribed. This can be due to side-effects that may present with the use of chronic medication.

Patients that suffer from a chronic condition have lower adherence to their medication than patients that are only receiving acute treatment (Osterberg & Blaschke, 2005:487). This is due to the longer duration of the period of treatment. Chronic patients' adherence can be measured in a pharmacy by calculating the refill adherence rate. This is defined as the percentage of the prescribed medication that the patient has actually taken over a period of time (Osterberg & Blaschke, 2005:487).

In the case of asthma adherence among chronic patients is very low. According to Bester and Hammann (2008:21) asthma has the second worst compliance out of the 27 diseases on the Chronic Disease List (CDL). Only 29.8% of patients with asthma were adherent to their medication in 2007. Patients with asthma also seem not to persist with their asthma medication over longer periods of time, with 61.5% of asthmatics persisting with their therapy for 12 months or longer.

Non-adherence has a direct correlation with morbidity in asthma (Bauman *et al*., 2002:6). Patients that admitted to non-adherence with their asthma medication experienced worse morbidity.

2.7.1 Reasons for non-adherence

Controller medication

Patients often use their inhalers for longer than one month. This happens especially if the patient does not use the controller medication as indicated to prevent asthma attacks (Bester & Hammann, 2008:20). Particularly in the case of the inhaled corticosteroids, patients tend to be non-adherent and to misunderstand the role of the inhaled corticosteroids in their asthma

therapy (Horne, 2006:67S; LaForest *et al*., 2009:1372). Patients seem to think that their asthma treatment is only symptomatic and if they experience no symptoms, they do not need to use their preventative medication. Therefore, they need to be provided with clear reasons why they should continue with their controller therapy even in the absence of asthma symptoms. Inhaler technique also plays an important role in the non-adherence of asthmatic patients (Horne, 2006:67S). A very small percentage of the dose of an inhaled corticosteroid reaches the lungs, because of patient non-adherence and because patients find it difficult to use the inhaler correctly (Cochrane *et al.,* 2000:545). Inhaler technique is also dependent on the type of inhaler the patient is using. Patients using Rotohalers and metered dose inhalers (MDI) were less adherent to their medication than patients using Turbuhalers and Diskhalers and had a more inadequate technique. Children with asthma find it especially difficult to use inhalers correctly (Volovitz *et al*., 2000:491). Patients using a spacer with their MDI had a much better technique and results than the patients using an MDI alone (Cochrane *et al*., 2000:547). Spacers also have the benefit that they increase the dose that reaches the lungs and prevent particles from only reaching the oropharynx (Chrystyn, 1997:18). The patients that use spacers with their MDI also experience fewer side-effects than when only the MDI is used. In a study done by Goldberg *et al.* (1996:234), it was shown that children that use a spacer with their inhaled corticosteroids were less likely to develop adrenal suppression due to systemic absorption of the corticosteroids, than children that used an MDI only.

Rand *et al*. (2007:923) found that patients were more likely to use their controller medication if the dose required was once a day, rather than twice a day. This links to the fact that oral controller medication adherence is better than inhaled medication adherence (Volovitz *et al.,* 2000:501). Patients prefer taking a tablet rather than using an inhaler, because it is easier, the dosage frequency is often less than for inhalers and it seems less embarrassing to the patient to take a tablet than to use an inhaler (Price & Kemp, 1999:682; Rand *et al.*, 2007:923).

Side-effects

Patients' perception of the side-effects they will experience during treatment has an influence on their adherence to the medication. In particular, treatment with inhaled corticosteroids seems to present a problem with patients, because they are afraid of the dangers of using too much corticosteroid (Horne, 2006:69S). Patients that are instructed to use inhaled corticosteroids for the first time and without having used them before tend to have misconceptions about the corticosteroids (Boulet, 1998:589). They believe it can cause mass gain, inhibit growth, make bones more vulnerable to fractures and cause them to build big muscles. Oral candidiasis and dysphonia are local side-effects that have a negative effect on patients' adherence (Murphy, 2007:189). A decline in efficacy is also a concern that patients using inhaled corticosteroids have. These fears that patients may have are not always

grounded, because Boulet (1998:589) found in a study done among Canadian patients, that 75% of the patients did not discuss their concerns about the corticosteroids with their physician or another health care professional.

Side-effects with the β_2-agonists are rare and usually dose-related and are not as troublesome to patients (Murphy, 2007:163; Rossiter, 2010:537). Inhaled therapies with the bronchodilators are less likely to cause side-effects than parenteral or oral therapies and since this is the most common route of administration for these drugs, patients are prepared to take them. The most common side-effects with the β_2-agonists are muscle tremors and cramps and this presents a problem to elderly patients (Murphy, 2007:164). Non-adherence for β_2-agonists and other quick relief medications vary in individuals and from day to day (Walders *et al*., 2005:181). They can be either underused, where the patient is well-controlled on their controller medication or overused when the patient is in need of rescue therapy several times per month. An over reliance on quick-relief medication may therefore suggest non-adherence to controller medication (Walders *et al*., 2005:182).

Other factors influencing adherence

Patient adherence is complex and an imperative part of it involves the patient's perception of the medication and the benefits that are connected to their adherence (Cochrane *et al*., 1999:765). A patient's perception is linked to other predisposing factors, such as socio-economic status and level of education (Van Dellen *et al*., 2008:757; Cochrane *et al*., 1999:765). In a study done by Horne and Weinman (1999:563) among British patients with chronic illnesses from four illness groups, it was found that differences in patient adherence were determined by three factors. They are the patient's attitude towards their medicines, the type of illness the patient has and the patient's age. They found that a patient's medication beliefs and attitude towards taking their medicines were more accurate predictors of their adherence than clinical factors. The majority of patients knew that the medication was necessary to maintain their health, but they had concerns over the adverse effects of the medication (Horne & Weinman, 1999:564). The different diseases had a different outcome on adherence. Asthma and cardiac patients were less adherent to their medication than the renal and cancer patients because, as the patients explained, they were more concerned about the adverse effects of the medication than the necessity of it (Horne & Weinman, 1999:564). Lastly, younger patients proved to be less adherent to their medication than older patients (Horne & Weinman, 1999:564).

Asthma patients need to be educated about their medication to avoid them jumping to wrong conclusions that will cause them not to use their medication to maintain control over their asthma correctly (LaForest *et al*., 2009:1374; Van Dellen *et al*., 2008:762; Cochrane *et al*., 1999:767).

2.7.2 Paediatric adherence and asthma

Paediatric adherence depends on the involvement of the child's caregiver and his/her commitment to adhere to the child's asthma treatment (Osterberg & Blaschke, 2005:494). Children with asthma that receive help and positive influences from their parents or caregivers to use their controller medication, tend to be more adherent to their therapy (Van Dellen *et al*., 2007:762). McQuaid *et al*. (2003:324) suggest a division of the asthma tasks between the parent or caregiver and the child. How these tasks are divided depends on the child's ability to understand the need and principles behind adequate asthma control therapy. When the child is still very young and does not possess the skills or ability to take on responsibility to adhere to medication requirements, the parent or caregiver should be primarily responsible for the child's asthma therapy. An interesting trend was seen in this study (McQuaid *et al*., 2003:329). Older children seem to be less adherent to their medication than younger children, although they are supposed to know more about their disease and are more capable of understanding how to use their medication and what it is for. This may be due to the children being less motivated and, without supervision from their caregiver, less able to keep in mind to use their medication daily. On the other hand, children who are given the responsibility to monitor their own medicine usage can choose to reduce the doses or skip doses to experiment with the efficacy of their medication.

Very few caregivers will admit to non-adherence according to a study done by Bauman *et al*. (2002:6) among children aged 4 to 9 years who had asthma and their caregivers in the Unites States. Paediatric patients and their caregivers have certain risk factors that make them more susceptible to non-adherence, such as concerns about side-effects of medications, more than one prescribed item for asthma that has to be used daily, the child's refusal to take the medication and concerns that the child may be getting too little or too much medicine (Bauman *et al*. 2002:4). These risk factors and the admittance of non-adherence to the child's asthma medication, lead to a higher morbidity of asthma. The children missed twice as much school, experienced more days of wheezing and impaired activity and had poorer overall functioning.

Paediatric adherence is therefore a complicated part of asthma therapy, because of the influence the child's parents and caregivers also have on the subject. By monitoring the adherence to asthma medication a child may experience less exacerbations and less absenteeism from school because of the hindrances of asthma. This could lead to an improvement in the quality of life of the patients.

2.7.3 The burden of asthma

Asthma creates a significant burden on patients on several levels. Patients have to put a considerable amount aside to be able to afford the medication every month and it has an impact on their quality of life as well (Ungar *et al.*, 2005:360; Fuhlbrigge *et al*., 2002:1044).

Asthma has very high costs associated with the treatment (Bahadori *et al*., 2009:38). The total expenditure for asthma in the United States is estimated to be between $12 and $14 billion and in Australia it is between $720 and $800 million annually (Edwards, 2004:60). It is ranked as one of the ten most expensive conditions and together with chronic obstructive pulmonary disease caused the public to spend $54 billion in 2005 in the United States (AHRQ, 2008).

The costs can be divided into direct and indirect costs. The direct costs of asthma include the tangible costs associated with hospital and emergency visits, physician visits and drugs and devices used in treatment. Indirect costs are also known as morbidity costs and concern loss of productivity, travelling and waiting time to physicians and hospitals and particularly absenteeism from work in adults and school days in children (Bahadori *et al*, 2009:27; Wang *et al.,* 2005:2).

The costs of asthma and patient adherence cannot be separated (Green, 2006:47; Fuhlbrigge *et al*., 2002:1048). One of the main goals of asthma treatment is to control asthma to such an extent that hospital admissions and emergency visits should not have to occur. By adhering to treatment guidelines and practising discipline, patients will be able to save money that would have been used for hospital and physician visits. Asthma treatment can therefore become cost-effective to patients if they choose to use medication correctly and pay attention to adherence.

In many areas of the world, patients with asthma do not have access to medication (Masoli *et al*., 2004:1). This is simply because these countries do not have the resources to be able to acquire the expensive medications that are used in asthma treatment. The Report on Poverty and Chronic Diseases in South Africa (Bradshaw & Steyn, 2002:108) established that poor patients use less asthma medication than richer patients, however, the morbidity of asthma is the same in both groups. Therefore, the reason for worse adherence and usage of asthma medications in poor patients are the high costs that are associated with asthma treatment.

2.8 Chapter summary

In this chapter asthma as a disease was discussed. It is a chronic disease that is typified by frequent attacks of breathlessness and wheezing. The underlying inflammation of the airways is a key feature of clinical asthma. Currently it is the most common chronic disease in children. Its diagnosis and treatment guidelines were discussed, with special focus on paediatric patients. There are two classes of drugs that are used to treat asthma, namely bronchodilators and anti-asthmatics. The future of asthma therapy looks promising and new drugs are being developed to treat patients more effectively and conveniently. The prevalence of asthma and paediatric asthma is increasing globally as well as in South Africa. Factors such as geographical location, gender of the patient and treatment by a general practitioner or a specialist have an influence on the prevalence of asthma. Patients with asthma are not adherent to their medication. Reasons for this are their misconceptions about controller medication, side-effects of the medication and inadequate patient education. The costs involved in treating asthma has an impact on patient adherence and the global economic burden of asthma is increasing. This can be slowed down by emphasising the importance of patients' adherence to their controller medication. Paediatric asthma treatment plays an important part in overall paediatric health care, because of the high prevalence of the disease.

In the next chapter the methodology and drug utilisation review and its application in this study will be discussed.

CHAPTER 3

Research methodology

3.1 Introduction

In this chapter the research methodology that was followed in this study will be discussed. The research objectives, empirical study, research design, data source, study population, editing and coding of the data, statistical analysis, reliability and validity of data and ethical considerations will be discussed.

3.2 General research objective

The general objective of the study was to determine the prescribing patterns of asthma products in South Africa with special reference to children up to 11 years.

3.3 Specific research objectives

3.3.1 Empirical research objectives

The specific research objectives of the empirical study were as follows:

- Determine the prevalence of asthma in a section of the private health care sector of South Africa according to various demographical factors such as age and gender.
- Determine the prescribing patterns and cost of asthma medication according to therapeutic category, active ingredient and trade name.
- Determine the prevalence of asthma in children according to gender and geographical area in a section of the private health care sector.
- Determine the costs associated with paediatric asthma medication in a section of the private health care sector of South Africa.
- Investigate the prescribing patterns of asthma medication to paediatric patients according to gender, therapeutic category, active ingredient, trade name and prescriber (general practitioners, pulmonologists and paediatricians).
- Review the prevalence of the prescribing of antibiotics and/or systemic corticosteroids together with asthma therapy.
- Investigate the paediatric patients' refill-adherence rate to certain asthma medication.

3.4 Empirical study

3.4.1 Research design

The research was done on the data that were extracted from a medicine claims database of a pharmaceutical benefit management company (PBM). Data were collected after the claims had been processed and the medicine dispensed to the patients. Therefore the study is a retrospective drug utilisation review.

A drug utilisation review study was defined by WHO in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (Sjöqvist & Birkett, 2003:77). Its main goals are to gain control over inappropriate prescribing, to reduce drug costs through different review processes and to facilitate the rational use of drugs in populations (Guo *et al*., 1995:1175; Sjöqvist & Birkett, 2003:78). Drug utilisation studies can be prospective, concurrent or retrospective (Soumerai & Lipton, 1995:1641; Guo *et al.,* 1995:1175).

A retrospective drug utilisation review is done after medications had been dispensed (Hennessy *et al*., 2003:1494). This aims to identify inappropriate prescribing patterns and it is valuable to determine the effectiveness of drugs (Sjöqvist & Birkett, 2003:81). Conclusions can then be made from the prescribing patterns that were identified and recommendations and interventions can be made to improve prescribers' habits towards certain medications.

3.4.2 Data source

The data for this study were extracted from a medicine claims database of a PBM in South Africa. The PBM manages the administration of medical benefits of 38 medical scheme and four capitation provider clients, and currently 1.5 million South Africans are beneficiaries. The data obtained were for a period of four years from 1 January 2005 to 31 December 2008. The data were analysed in periods of 12 months at a time.

The following fields were used in the study:

- Date of dispensing the prescription
- Medical scheme member and dependant identification code
- Final prescription cost
- Date of birth of the patient
- Gender of the patient
- Pharmacological subsections according to the MIMS®

- NAPPI codes
- NAPPI code extension
- NAPPI code description
- Prescriber type
- Postal code of the prescriber's practice
- Days medication was supplied

3.4.3 Study population

The asthma study population was composed in the following manner:

- Patients that had used medication for asthma as classified by MIMS® groups 10.2 (bronchodilators) and 10.4 (anti-asthmatics) (Snyman, 2009a:14a). It was essential that patients had to use at least one type of medication from any one of these groups.
- Patients that fall under the following age groups were used to determine the paediatric asthma population:
    - ❖ 0 – 4 years
    - ❖ > 4 ≤ 11 years

Patients that were older than 11 years were considered as adults and not included in the paediatric study population.

The asthma study population was extracted from the total population. The total population contained a total number of 5220804 patients and asthma patients made up 24.03% (n= 1254397 patients) of this total from 2005 to 2008.

3.4.4 Editing and coding of data

During this study the data were divided into different categories.

3.4.4.1 The NAPPI code

These are unique product codes that are implemented to simplify electronic transactions. It is usually a nine digit code, that incorporates the product name, pack size, strength and manufacturer (Snyman, 2009a:8a). For example, the NAPPI code for Singulair® 4mg chewable tablets is 700251001.

3.4.4.2 The MIMS® classification system

The MIMS® classification system is based on dividing pharmaceutical products into groups according to their pharmacological action (Snyman, 2009a:13a). For the purpose of this study groups 10.2 (bronchodilators), 10.4 (anti-asthmatics), 18 (anti-microbials) and 19.5 (corticosteroids) were used.

3.4.4.3 Age

Age is calculated from a person's date of birth. In this study it was possible to calculate the age of a patient from the date of birth that was indicated on the prescription that was claimed through the medicine claims database. The age of the patient was calculated from 1 January of the year following the date that the prescription was dispensed. For example, if the prescription was dispensed to a child in October 2005, the age of the child would be taken as the age of the child as on 1 January 2006.

The age groups in this study were divided into the following categories, according to the NHLBI (2007):

- 0 – 4 years
- > 4 ≤ 11 years
- > 11 years

3.4.4.4 Gender

The WHO (2010) defines gender as "the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women". For the purpose of this study gender will be used to determine whether the prescription was dispensed to a male or a female.

3.4.4.5 Prescriber type

According to the Medicines and Related Substances, Act 101 of 1965 (South Africa, 1997:22) an authorised prescriber is a medical practitioner, dentist, veterinarian, practitioner, nurse or other person that is registered under the Health Professions Act of 1974. This study aimed to determine whether the type of prescriber would have an influence on the type of medicine items that are prescribed to an asthma patient. A distinction was made between the following prescribers:

- General practitioners
- Pulmonologists

- Paediatricians
- Other specialists

3.4.4.6 Geographical area

The location of the prescriber's practice according to the database helped to determine in which area the prescription had been dispensed to the patient. Patients in urban areas generally are more exposed to pollutants and this has an influence on the prevalence of asthma and overall respiratory health of patients in those areas (O'Connor *et al*., 2008:1135).

3.4.5 Measuring instruments

The following instruments were used to analyse the data:

3.4.5.1 Prevalence

Prevalence can be defined as the probability that a condition exists in a specific population or the probability of the occurrence of a disease (Waning & Montagne, 2001:21). For the purpose of this study prevalence and the number of asthma patients, prescriptions and medicine itemswere viewed as equivalents, depending on the type of prevalence that was being determined.

In the following chapter the prevalence of asthma will be determined in the following categories:

- The prevalence of all prescriptions and medicine items claimed through the database by all patients from January 2005 to December 2008.
- The prevalence of all asthma prescriptions and medicine items claimed through the database by asthma patients from January 2005 to December 2008.
- The prevalence of all asthma prescriptions and medicine items in asthma patients under 11 years of age from January 2005 to December 2008.
- The prevalence of all asthma prescriptions and medicine items in asthma patients under 11 years of age according to gender, geographical area, type of prescriber and therapeutic category, active ingredient and trade name of medication from January 2005 to December 2008.
- The prevalence of all asthma prescriptions in patients under 11 years of age in combination with other asthma medications (MIMS® group 10.2 & 10.4), antimicrobials (group18) and corticosteroids (group 19.5).

3.4.5.2 Cost

Costs of medication are responsible for the single highest direct cost involved in the economic burden of asthma (American Lung Association, 2010). In this study cost was expressed as a rand-value (R) and the focus was only on medication cost claimed through the PBM.

In the following chapter the cost of medicines will be determined for the following categories:

- The cost of all medicine items claimed through the database from January 2005 to December 2008.
- The cost of all asthma medicine items claimed through the database from January 2005 to December 2008.
- The cost of all asthma medicine items in patients under 11 years of age from January 2005 to December 2008.

3.4.5.3 Refill-adherence rate

Patients that suffer from a chronic condition have lower adherence to their medication than patients that are receiving acute treatment only (Osterberg & Blaschke, 2005:487). For the purpose of this study certain individual asthma products' refill-adherence will be followed. Patients that get their prescription filled 10 times or more during a period of twelve months are considered to be adherent to their medication. This is an important aspect as only an estimated 29.8% of asthma patients are considered to be adherent to their medication.

The refill-adherence rate was calculated per individual asthma product (trade name) presented to a specific patient by using the following formula:

$$\textit{Refill-adherence rate} = \frac{\textit{Total days supply - Days supply of the last prescription}}{\textit{Days between refills}} \times \frac{100}{1}$$

The days between refills were calculated as follows:

$$\textit{Days between refills} = \textit{Date of last prescription - Date of first prescription}$$

Certain criteria were set for the refill-adherence rate. It was calculated per trade name per patient for 2005 to 2008. If a patient had received only one prescription during this time the prescription was not brought into the calculations. Only the asthma medication trade names that were used continuously on a monthly basis were considered, in other words, those

products that have a month's supply of doses or tablets per device or packet. The criteria for what is considered adherent were also set:

- Adherence rate ≤ 90% = Unacceptable low refill-adherence
- 90% < Adherence rate ≤ 110% = Acceptable refill-adherence
- Adherence rate ≥ 110% = Unacceptable high refill-adherence

3.5 Statistical analysis

The following statistical methods were used to investigate the data:

3.5.1 Average value (mean)

The average value or arithmetic mean is the average usually used to calculate a test average (Brase & Brase, 1999:94). It is the sum of the of the observations divided by the number of observations (Samuels & Witmer, 1999:32). It was calculated as follows:

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

Where:

x = the values of the variable

$\sum$ = the sum

n = number of observations

3.5.2 Standard deviation

The standard deviation is the difference between an observation or data entries and the sample mean (Samuels & Witmer, 1999:49; Brase & Brase, 1999:103). It was calculated as follows:

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

Where:

s = standard deviation

x = value of the variable

$\bar{x}$ = arithmetic mean

n = number of observations

3.5.3 Effect sizes / *d*-values

The effect size or *d*-value can be defined as the degree by which two mean values differ divided by the largest standard deviation of the two means (Cohen & Lea, 2004:60; Cohen, 1988:24). It was calculated as follows:

$$d = \frac{\overline{x_a} - \overline{x_b}}{s_{max}}$$

Where:

d = effect size

$\overline{x_a}$ = average cost value of a

$\overline{x_b}$ = average cost value of b

s_{max} = the largest standard deviation between the two averages

According to Cohen (1988:3) the following guidelines for *d*-values can be set:

***d* = 0.2** - small effect (not significant)

***d* = 0.5** - medium effect (observable and may be practically significant)

***d* = 0.8** - large effect (significant and of practical importance)

The *d*-value was used to express the degree of difference between the cost of prescriptions written by the different prescribers.

3.6 Reliability and validity of the research instruments

The data were obtained from a medical claims database. There was no direct manipulation of the data done by the researcher. The research done was performed from the perspective that all data acquired from the medicine claims database were reliable and valid. The data for analysis were, however, obtained from one medicine claims database only, therefore external accuracy is limited and the results can be generalised to the allocated database and study population that were used in this study only.

3.7 Ethical considerations

All patient, medical practice, pharmacy or medical scheme information was kept confidential by the PBM and the researcher did not have access to such information. Permission to perform this study was granted by the PBM's board of directors and by the North-West University's Ethical Committee. The North-West University approved the study as a sub-project under the "Investigation of medicine usage patterns in a section of the private health care sector utilising data from a Pharmaceutical Benefit Management (PBM) in South Africa" project. The ethical committee granted the study the following permission number: NWU-0046-08-S5.

3.8 Chapter summary

The research methodology was discussed in this chapter. The general and specific objectives, research design, data source, study population and measuring instruments were discussed.

In the following chapter the results from the empirical investigation will be documented.

CHAPTER 4

Results and discussion

4.1 Introduction

In this chapter the results of the empirical study will be discussed. The usage and prevalence of asthma treatment and particularly asthma treatment in children in South Africa, for the study period from 1st January 2005 to 31st December 2008 will be reported and discussed. The data were analysed in periods of 12 months at a time.

For the purpose of this study the total database was analysed in terms of number of patients, prescriptions, medicine items and cost per year. The asthma medicine items were extracted from the total database according to the MIMS® classification system (groups 10.2 and 10.4) (Snyman, 2009a:14a). These are the bronchodilators and anti-asthmatics respectively.

The focus of this study is on paediatric asthma, therefore children under the age of 11 years were of special interest (NHLBI, 2007:72). Patients were divided into different age groups:

- 0 – 4 years
- > 4 ≤ 11 years
- > 11 years

The literature review has proved that asthma has a significant prevalence among children globally and in South Africa (Masoli *et al.,* 2004:9 ; Zar *et al.*, 2007:560). The aim of this study was to confirm the prevalence of paediatric asthma in South Africa and to identify the prescribing patterns of asthma medication in a section of the private health care sector.

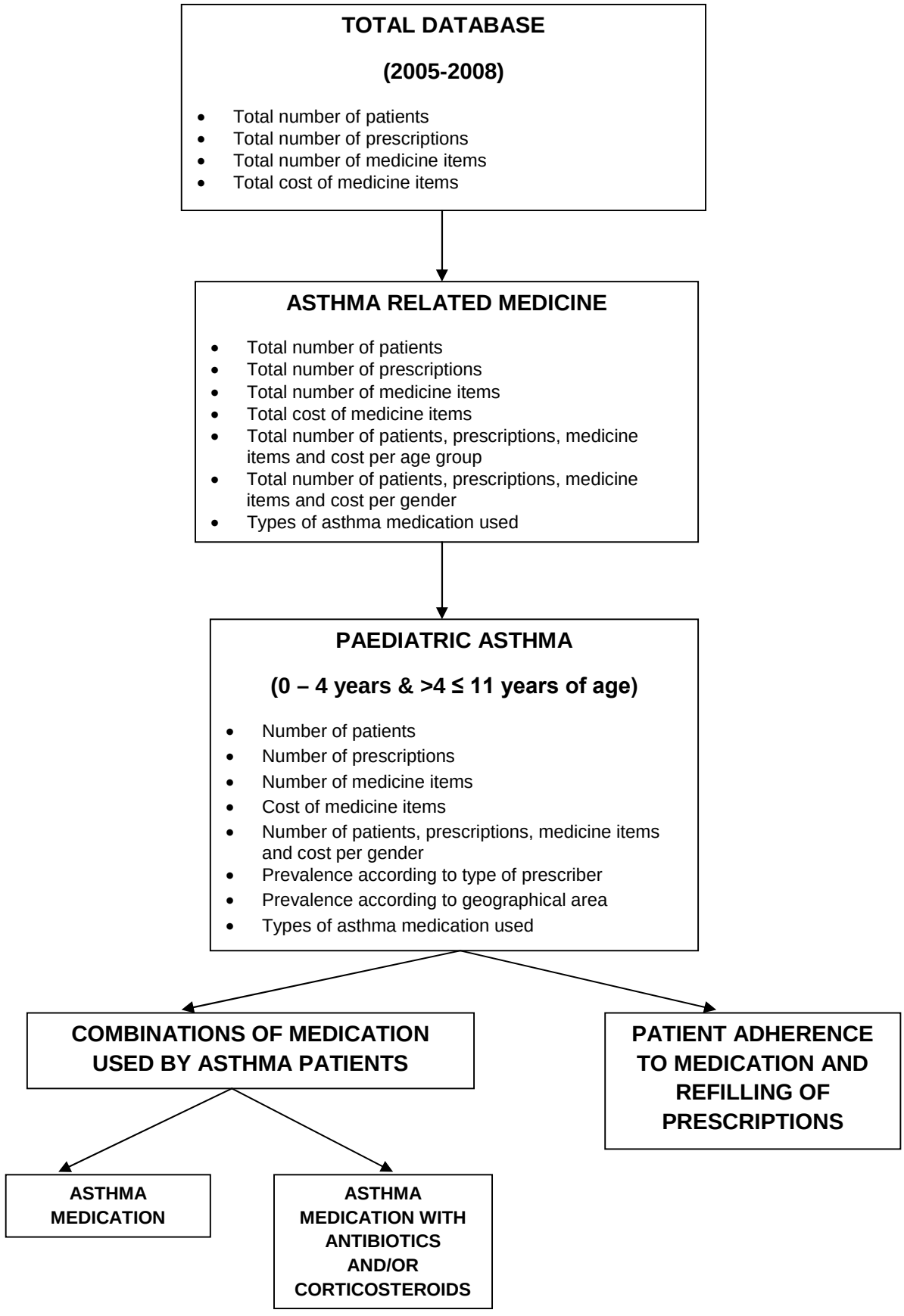


Figure 4.1: Organogram of the presentation of the data in chapter 4

4.2 Terms and definitions

The following terms need to be explained for the purpose of this study:

4.2.1 Patient

This is the person who receives medical attention and to whom the prescription was issued. The patient is treated for a medical condition, which could include asthma. The patient is the person who claims the prescription.

4.2.2 Prescription

A prescription is a list of medicine items and instructions issued to the patient by an authorised prescriber. The patient then claims the prescription at a pharmacy. Asthma medication may be included in the medicine items that may appear on the prescription.

4.2.3 Medicine items

A medicine item contains an active ingredient used in the treatment of diseases, which may include asthma. Medicine items appear on the prescription and are claimed accordingly by the patient.

4.2.4 Asthma medication

Asthma medication is medication that is associated with the treatment of asthma. For the purpose of this study asthma medication includes the bronchodilators and anti-asthmatics (listed as groups 10.2 and 10.4 in MIMS® respectively) (Snyman, 2009a:14a). The asthma database also refers to medication from group 10.2 and 10.4.

4.2.5 Study population

The study population consisted of the prescriptions that were claimed for the specific study period via the medicine claims database. The total database consisted of all the prescriptions claimed through the database during 1 January 2005 until 31 December 2008. The asthma database only consisted of prescriptions that had medicine items from the asthma medication category listed.

4.2.6 Paediatric patients

For the purpose of this study, a child's age was defined as a person between the ages of 0 – 11 years of age. This age group was divided into two smaller groups, the first ranging from 0 – 4 years of age and the second from 5 – 11 years of age (NHLBI, 2007:72).

4.2.7 Prescriber

An authorised prescriber can be defined as a medical practioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974 (South Africa, 1997:22). For the purpose of this study certain authorised prescribers were identified. These were general practitioners, paediatricians, pulmonologists and other prescribers that may have prescribed asthma medication.

4.2.8 Geographical area

The term geographical area as used in this dissertation is defined as the location of the prescriber of the prescription's practice according to postal code. From this information, the prescriptions could be divided according to province, which was of use in this study.

4.2.9 Active ingredient

According to the FDA (2010) the definition of an active ingredient is any product that supplies man or animals with pharmacological activity or other effects in the progress of a disease. For the purpose of this study, the active ingredients that were involved in the treatment of asthma were discussed.

4.2.10 Trade name

The trade names of the asthma medication that were used were classified according to NAPPI codes that are listed in the MIMS® under groups 10.2 and 10.4. This gives every registered product a unique code which is available on the database.

4.2.11 Combination products

For the purpose of this study a combination product is defined as one asthma product that contains two active ingredients, for example ipratropium/salbutamol or bromhexine/orciprenaline. It is classified as one product and should be distinguished from "combinations" or "combination therapy".

4.2.12 Combinations

Combinations, for the purpose of this study, included more than one product prescribed to a patient. In the case of this study it is usually an asthma product together with another asthma product, an antibiotic or corticosteroid.

4.3 Overview of the total database

Table 4.1 provides the general prescribing patterns of the total database from 1 January 2005 to 31 December 2008.

Table 4.1: General prescribing patterns of the total database for the years 2005 to 2008

Year	Total number of patients	Total number of prescriptions	Total number of medicine items	Total expenditure on medicine items (R)
2005	1509621	8391836	19500774	1 819 865 251.63
2006	1558090	8906348	21113422	1 959 738 734.09
2007	1178596	7911096	19075724	1 918 284 176.00
2008	974497	6775873	16439253	1 785 871 013.85

There was an increase in total number of patients, total number of prescriptions, total number of medicine items and total expenditure from 2005 to 2006. A decrease from 2006 to 2007 followed and a further decrease was seen in 2008 (refer to table 4.1 and figure 4.2).

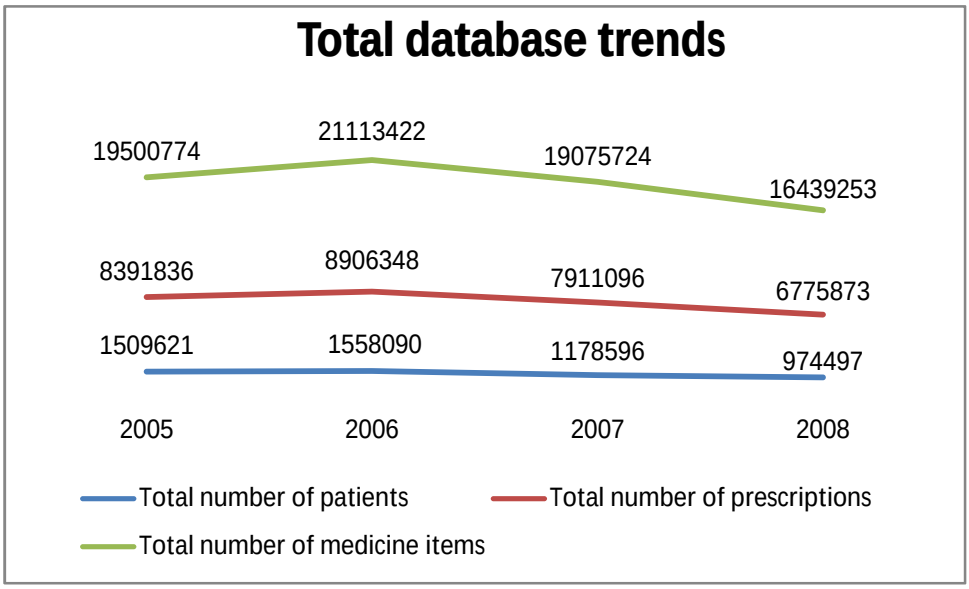


Figure 4.2: Trends from the total database according to total number of patients, prescriptions and medicine items.

4.3.1 General prevalence of asthma

The general prevalence of asthma compared to the total database can be seen in table 4.2.

The percentage of patients that claimed asthma medication showed a steady increase from 2005 (23.01%) to 2008 (30.16%) as a percentage of the total number of patients on the total database, although the number of patients decreased from 2005 (n=347342) to 2008 (n=293916).

The total number of prescriptions for asthma medication as a percentage of the total database showed an increase from 2005 (7.68%) to 2006 (7.85%), but then a decrease to 2008 (7.16%). This may be due to the total number of asthma patients on the total database that showed a clear decrease from 2005 to 2008 (refer to table 4.1).

The total number of asthma items as a percentage of the total number of medicine items on the total database also reflects the increases and decreases from the total database. It is the same pattern that can be observed for the total number of prescriptions. The percentage of the number of asthma medicine items for 2005 (n=801277) to 2008 (n=611139) showed a decrease of 0.39%.

Table 4.2: General prevalence of asthma represented as part of the total database

Year		Number of patients	Number of prescriptions	Number of medicine items
2005	**Total database**	1509621	8391836	19500774
	Asthma database	347342	644143	801277
	%Prevalence of asthma*	**23.01%**	**7.68%**	**4.11%**
2006	**Total database**	1558090	8906348	21113422
	Asthma database	372285	699473	874184
	%Prevalence of asthma*	**23.89%**	**7.85%**	**4.14%**
2007	**Total database**	1178596	7911096	19075724
	Asthma database	293916	576490	725528
	%Prevalence of asthma*	**24.94%**	**7.29%**	**3.80%**
2008	**Total database**	974497	6775873	16439253
	Asthma database	240854	484983	611139
	%Prevalence of asthma*	**24.72%**	**7.16%**	**3.72%**

* %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year multiplied by 100. This is done for number of patients, prescriptions and medicine items.

4.3.2 Medication cost of asthma

Table 4.3 indicates what part of the total expenditure on the medical database was made up of asthma medication expenditure. This can be seen as the total cost of asthma medicine items per year for this study, i.e. medication that was classified under 10.2 and 10.4 in MIMS® (Snyman, 2009a:14a). The data only included the medication claim information, thus hospitalisation costs were not included in this data. Asthma expenditure as part of the total expenditure for all medicine items claimed showed a steady decrease from 2005 to 2008. This could be due to generic equivalents of items that were made available during the study period that proved to be less expensive or due to the fact that overall expenditure decreased from 2005 to 2008 (refer to table 4.1).

Table 4.3: General cost of asthma represented as part of the total database

Year	Total expenditure (R)	Asthma expenditure (R)	% Asthma expenditure*
2005	1 819 865 251.63	84 376 592.80	4.64%
2006	1 959 738 734.09	88 767 589.07	4.53%
2007	1 918 284 176.66	81 726 421.88	4.26%
2008	1 785 871 013.85	74 140 653.80	4.15%

* %Asthma expenditure is calculated by dividing the asthma expenditure by the total expenditure for the specific year multiplied by 100.

4.4 Prevalence of asthma

4.4.1 Number of patients

In table 4.2 a clear upsurge can be seen in the percentage of asthma patients out of the total database from 2005 to 2008. This occurred besides the fact that the number of patients showed a decrease.

From 2005 to 2008 the prevalence of asthma patients increased with 1.71%. By the end of 2008 patients that received asthma medication made up 24.72% (n=240854) of the total database (n=974497). This showed that asthma was a significant disease among patients in this section of the private health care sector, as so many of them received medication to aid their asthma or other respiratory conditions (refer to table 4.2).

4.4.2 Number of prescriptions

Table 4.4 indicates the number of prescriptions that were dispensed and claimed through the medical claims database from 2005 to 2008. There was an increase in the number of prescriptions from 2005 (n=644143) to 2006 (n=699473), which was followed by a decrease in 2007 (n=576490) and a further decrease in 2008 (n=484983). This correlated with the patterns seen with the number of prescriptions on the total database. The prevalence of asthma as a percentage of all the prescriptions on the total database also displayed this trend. The total number of prescriptions for asthma medication increased with 8.59% (n=55330) from 2005 to 2006 and decreased by 30.66% (n=214490) from 2006 to 2008.

The number of prescriptions per patient per year showed a steady increase. The increase according to the asthma database showed that patients were claiming more prescriptions with asthma medication on per year, from 1.85 ± 2.20 prescriptions in 2005 to 2.01 ± 2.47 in 2008. On average a patient received 2 or 3 prescriptions per year for asthma medication (refer to table 4.4). If a patient were to be a chronic asthmatic though, this would be a worrying average, because asthma sufferers should refill their prescription at least 10 times per year in order to be adherent (Bester & Hammann, 2008:20). This is, however, subject to change (refer to section 4.7) and depends on different factors. In this case the average could have been brought down by patients that were not asthmatic and only received medication

from groups 10.2 and 10.4 for one month or less. The reason that the numbers in the total database are much higher could be due to the prescriptions that could have been claimed as chronic or acute medicine. Patients on chronic medication fill more prescriptions per year on average than patients that only claim acute medicine sporadically.

Table 4.4: Number of prescriptions according to the total and asthma database

Year		Number of prescriptions	Number of prescriptions per patient per year
2005	**Total database**	8391836	5.56 ± 6.75
	Asthma database	644143	1.85 ± 2.20
	% Prevalence of asthma*	**7.68%**	
2006	**Total database**	8906348	5.72 ± 6.96
	Asthma database	699473	1.88 ± 2.22
	% Prevalence of asthma*	**7.85%**	
2007	**Total database**	7911096	6.71 ± 7.55
	Asthma database	576490	1.96 ± 2.37
	% Prevalence of asthma*	**7.29%**	
2008	**Total database**	6775873	6.95 ± 7.85
	Asthma database	484983	2.01 ± 2.47
	% Prevalence of asthma*	**7.16%**	

* %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year multiplied by 100.

4.4.3 Number of medicine items

In table 4.5 the number of asthma medication items in relation to the total database can be observed. The percentage prevalence of asthma items showed the same trend as the number and prevalence of asthma prescriptions.

Regarding the number of medicine items that appeared on a prescription, the total database showed that there were on average 2 or 3 items on a prescription. The asthma database, however, indicated an average of 1 or 2 items per prescription that appeared in groups 10.2 and 10.4.

It may be that many types of asthma medications were not prescribed on the same prescription. The maximum number of items per prescription of the asthma database was significantly lower than that of the total database. This may be of importance when different prescribers of asthma medication are examined (refer to section 4.5.4).

Table 4.5: Number of items and number of items per prescription on the total and asthma database

Year		Number of medicine items	Number of medicine items per prescription	Minimum number of medicine items per prescription	Maximum number of medicine items per prescription
2005	**Total database**	19500774	2.32 ± 1.52	1	41
	Asthma database	801277	1.24 ± 0.55	1	7
	% Prevalence of asthma*	**4.11%**			
2006	**Total database**	21113422	2.37 ± 1.55	1	35
	Asthma database	874184	1.25 ± 0.56	1	9
	% Prevalence of asthma*	**4.14%**			
2007	**Total database**	19075724	2.41 ± 1.59	1	38
	Asthma database	725528	1.26 ± 0.57	1	8
	% Prevalence of asthma*	**3.80%**			
2008	**Total database**	16439253	2.43 ± 1.64	1	35
	Asthma database	611139	1.26 ± 0.57	1	8
	% Prevalence of asthma*	**3.72%**			

***** %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year multiplied by 100.

4.4.4 Prevalence according to age

Table 4.6 indicates the prevalence of asthma as a percentage of the total database. The asthma database was divided into three age groups to determine the prevalence of asthma among patients of different ages.

Table 4.6: Prevalence of asthma according to age groups

		0 – 4 years			> 4 ≤ 11 years			> 11 years		
Year		**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**
2005	**Total database**	76175	279560	694676	146334	440544	1095807	1287112	7671732	17710291
	Asthma database	29156	49006	58658	46037	77156	94403	272149	517981	648216
	%Prevalence of asthma*	**38.28%**	**17.53%**	**8.44%**	**31.46%**	**17.51%**	**8.61%**	**21.14%**	**6.75%**	**3.66%**
2006	**Total database**	74980	287345	726266	145048	453632	1140677	1338062	8165367	19246479
	Asthma database	30186	52380	63591	47157	82119	102001	294942	564973	708592
	%Prevalence of asthma*	**40.26%**	**18.23%**	**8.76%**	**32.51%**	**18.10%**	**8.94%**	**22.04%**	**6.92%**	**3.68%**
2007	**Total database**	50563	227126	579239	114219	382519	959273	1013814	7301439	17537212
	Asthma database	23349	42776	52911	36847	66521	83794	233720	467193	588823
	%Prevalence of asthma*	**46.18%**	**18.83%**	**9.13%**	**32.26%**	**17.39%**	**8.74%**	**23.05%**	**6.40%**	**3.36%**
2008	**Total database**	25464	111358	281110	86328	289540	712330	862705	6374965	15445813
	Asthma database	11306	21129	26246	28347	51684	64715	201201	412169	520178
	%Prevalence of asthma*	**44.40%**	**18.97%**	**9.34%**	**32.84%**	**17.85%**	**9.08%**	**23.32%**	**6.47%**	**3.37%**

***** %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year and age group multiplied by 100. This is done for number of patients, prescriptions and medicine items.

Overall it could be seen that the prevalence for the number of patients with asthma was highest among children between the ages of 0 and 4 years. The highest prevalence was seen in 2007 (46.18%). The prevalence of the number of prescriptions and number of medicine items showed an increase, which could indicate that asthma may be regarded as a growing problem among children younger than 4 years of age.

Children older than 4 years and younger or equal to 11 years of age (>4 ≤ 11 years) also showed a high prevalence. It was not quite as high as in younger children, but the prevalence of asthma patients between the ages of >4 ≤ 11 years remained above 30% from 2005 to 2008. The prevalence of the number of prescriptions and number of medicine items showed a slight increase, but the prevalence mostly remained constant. Paediatric asthma will be discussed in more detail in section 4.5.

Children above 11 years of age are regarded as adults when it comes to asthma treatment (NHLBI, 2007:72). Therefore the asthma prevalence must be seen in the context of adult diseases and that adults, especially elderly people, are more prone to different types of diseases, such as diseases associated with aging, for example osteoporosis and other degenerative diseases (Vellas *et al*., 1992:1226S). The prevalence of asthma among adults is therefore not as prominent as it is in children, which can be seen in table 4.6. The prevalence of the number of patients that used asthma medication is still cause for concern and may lead to the suggestion that asthma is not well-controlled among patients.

4.4.5 Prevalence according to gender

Table 4.7 shows that there were more female than male patients on the database. The prevalence of asthma medication usage was, however, higher among males according to number of patients, prescriptions and medicine items.

The highest prevalence among the patients was seen in 2007 in both males and females. The prevalence of the number of prescriptions and number of medicine items from the asthma database, showed the same trend as the total database (refer to figure 4.2).

The increase in prevalence in female patients was larger than the prevalence in male patients. The number of female patients decreased from 2005 (n=187918) to 2008 (n=131662), but the prevalence increased by 2.15%. Male patients also showed a decrease from 2005 (n=159025) to 2008 (n=109192) and although the prevalence of asthma medication usage was higher among males, the prevalence only increased with 1.13%.

Table 4.7: Prevalence of asthma according to gender

		Female			Male		
Year		**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**
2005	**Total database**	842386	5036494	11750190	665505	3348219	7734461
	Asthma database	187918	348521	431860	159025	294981	368609
	% Prevalence of asthma*	**22.31%**	**6.92%**	**3.68%**	**23.90%**	**8.81%**	**4.77%**
2006	**Total database**	868891	5336202	12699707	688091	3565328	8403158
	Asthma database	202945	380573	473545	169095	318496	400141
	% Prevalence of asthma*	**23.36%**	**7.13%**	**3.73%**	**24.57%**	**8.93%**	**4.76%**
2007	**Total database**	654348	4754911	11509346	523841	3154355	7562466
	Asthma database	160491	314339	394469	133364	262039	330931
	% Prevalence of asthma*	**24.53%**	**6.61%**	**3.43%**	**25.46%**	**8.31%**	**4.38%**
2008	**Total database**	538254	4062385	9893928	436243	2713478	6545325
	Asthma database	131662	265561	333660	109192	219421	277479
	% Prevalence of asthma*	**24.46%**	**6.54%**	**3.37%**	**25.03%**	**8.09%**	**4.24%**

***** %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year and gender multiplied by 100. This is done for number of patients, prescriptions and medicine items.

4.4.6 Prevalence of asthma medication usage according to types of medication

4.4.6.1 Bronchodilators versus anti-asthmatics

In table 4.8 the usage of the different types of asthma medication is compared. It is clear that bronchodilators were prescribed more often than anti-asthmatics. More than 80% of asthma medications dispensed from 2005 to 2008 were bronchodilators. This poses a possible problem area, because asthma patients are theoretically supposed to control their asthma with anti-asthmatic medication by using it daily (Department of Health, 2008:271). The positive aspect is, however, that the prevalence of the usage of anti-asthmatics has increased from 2005 to 2008 by 1.72%, although the number of medicine items dispensed on the asthma database decreased. The increase in the use of anti-asthmatics has led to a decrease in the use of bronchodilators, which is ideally what prescribing patterns should be.

Table 4.8: The ratio of bronchodilator to anti-asthmatic medication usage

Year	Number of medicine items (N)	%Bronchodilators*	%Anti-asthmatics**	Ratio of bronchodilators to anti-asthmatics***
2005	801277	**84.35%** (n=675896)	**15.65%** (n=125381)	**5.39 : 1**
2006	874184	**83.99%** (n=734224)	**16.01%** (n=139960)	**5.24 : 1**
2007	725528	**82.93%** (n=601668)	**17.07%** (n=123860)	**4.86 : 1**
2008	611139	**82.63%** (n=504991)	**17.37%** (n=106148)	**4.76 : 1**

***** %Bronchodilators is calculated by dividing the number of bronchodilator items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

****** %Anti-asthmatics is calculated by dividing the number of anti-asthmatic items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

*** Ratio of bronchodilators to anti-asthmatics is calculated by dividing the (n) of bronchodilators by the (n) of anti-asthmatics.

4.4.6.2 Therapeutic category

Table 4.9 indicates the difference in prescribing patterns according to the different therapeutic categories of the asthma medication. The following therapeutic groups were classified under bronchodilators (Group 10.2):

- Sympathomimetics
- Methylxanthines
- Anticholinergics
- Combination products

Anti-asthmatics (Group 10.4) included:

- Glucocorticoids
- Leukotriene receptor antagonists
- Other anti-asthmatics (Ketotifen)

Table 4.9: Prevalence of asthma medication according to therapeutic category

Year	Therapeutic category	Number of medicine items	%Prevalence of asthma medication*
2005	**Sympathomimetics**	185075	23.10%
	Methylxanthines	242850	30.31%
	Anticholinergics	23813	2.97%
	Combination products	224158	27.98%
	Glucocorticoids	90755	11.33%
	Leukotriene receptor antagonists	26337	3.29%
	Other anti-asthmatics	8289	1.03%
2006	**Sympathomimetics**	199654	22.84%
	Methylxanthines	256883	29.39%
	Anticholinergics	24947	2.85%
	Combination products	252740	28.91%
	Glucocorticoids	96682	11.06%
	Leukotriene receptor antagonists	35315	4.04%
	Other anti-asthmatics	7963	0.91%
2007	**Sympathomimetics**	148040	20.40%
	Methylxanthines	200154	27.59%
	Anticholinergics	22872	3.15%
	Combination products	230602	31.78%
	Glucocorticoids	79300	10.93%
	Leukotriene receptor antagonists	39252	5.41%
	Other anti-asthmatics	5308	0.73%
2008	**Sympathomimetics**	117181	19.17%
	Methylxanthines	167973	27.49%
	Anticholinergics	18925	3.10%
	Combination products	200912	32.88%
	Glucocorticoids	66910	10.95%
	Leukotriene receptor antagonists	35745	5.85%
	Other anti-asthmatics	3493	0.57%

* %Prevalence of asthma medication is calculated by dividing number of medicine items per therapeutic category per year by the total number of asthma medicine items that were dispensed multiplied by 100.

Certain types of therapeutic groups showed a decrease in usage. Sympathomimetics, such as β_2-agonists, decreased by 3.93% from 2005 (n=185075) to 2008 (n=117181). The usage of methylxanthines, theophylline and aminophylline, decreased from 30.31% in 2005 (n=242850) to 27.49% in 2008 (n=167973). This could be because theophylline is being phased out by prescribers because of its systemic side-effects (refer to section 2.5.2.2). The use of glucocorticoids alone declined by 0.38%, but they are also incorporated into combination products with sympathomimetics, which showed an increase of 4.9% from 2005 (n=224158) to 2008 (n=200912) and had the highest prevalence among all the therapeutic groups. Other asthmatics (ketotifen, according to MIMS® categorisation) are not being used often and the prevalence also showed a decrease from 2005 (n=8289) to 2008 (n=3493) of 0.46%.

The usage of leukotriene receptor antagonists, for example montelukast, started showing an increase. The treatment is recent compared to the other therapeutic groups, but has already showed an increase of 2.56% in prevalence.

The prevalence of anticholinergics did not show a significant change and table 4.9 shows that this group was not being dispensed often.

Table 4.10: Summary of increases and decreases of therapeutic groups from 2005 to 2008

Sympathomimetics	↓
Methylxanthines	↓
Anticholinergics	↑
Combinations	↑
Glucocorticoids	↓
Leukotriene receptor antagonists	↑
Other anti-asthmatics	↓

4.4.6.3 Active ingredient

4.4.6.3.1 Bronchodilators

Table 4.11: Prevalence of bronchodilators according to active ingredient during 2005

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Theophylline/Etophylline	168899	24.99%
2	Salbutamol	112009	16.57%
3	Bromhexine/Orciprenaline	105725	15.64%
4	Theophylline	68806	10.18%
5	Salmeterol/Fluticasone	51129	7.57%
6	Ipratropium/Salbutamol	28949	4.28%
7	Fenoterol	22976	3.40%
8	Fenoterol/Ipratropium	22347	3.31%
9	Budesonide/Formoterol	16661	2.47%
10	Salmeterol	13485	2.00%
11	Ipratropium	11861	1.76%
12	Formoterol	9624	1.42%
13	Tiotropium	6822	1.01%
14	Aminophylline/Ephedrine	2820	0.42%
15	Terbutaline/Guaifenesin	2800	0.41%
16	Hexoprenaline	2368	0.35%
17	Clobutinol/Orciprenaline	1677	0.25%
18	Other	26938	3.99%

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

In 2005, three of the top 5 active ingredients according to prevalence were combinations of asthma medications (group 10.2.4) (refer to table 4.11). Theophylline/etophylline and Bromhexine/orciprenaline are cough syrups with bronchodilator properties. This could have had an effect on the high prevalence, because the patient was not necessarily diagnosed with asthma when receiving these medications. The specific diagnosis of the disease was not available from the database. Salbutamol, theophylline and salmeterol/fluticasone are active ingredients that are effective against asthma and cause bronchodilatation.

Salbutamol, a β_2-agonist, is available in inhaler and oral dosage forms, which makes it convenient. The prevalence was 16.57% (n=112009) for all dosage forms in 2005. Salmeterol/fluticasone combination proved to be the highest ranked glucocorticoid containing active ingredient, which could be given as monotherapy to an asthmatic patient (7.56%).

Table 4.12: Prevalence of bronchodilators according to active ingredient during 2006

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Theophylline/Etophylline	180817	24.63%
2	Salbutamol	119399	16.26%
3	Bromhexine/Orciprenaline	117888	16.06%
4	Theophylline	70427	9.59%
5	Salmeterol/Fluticasone	59503	8.10%
6	Ipratropium/Salbutamol	32405	4.41%
7	Fenoterol	25337	3.45%
8	Fenoterol/Ipratropium	22083	3.01%
9	Budesonide/Formoterol	21085	2.87%
10	Salmeterol	13441	1.83%
11	Ipratropium	11992	1.63%
12	Formoterol	9353	1.27%
13	Tiotropium	8290	1.13%
14	Aminophylline/Ephedrine	3161	0.43%
15	Terbutaline/Guaifenesin	2781	0.38%
16	Hexoprenaline	2586	0.35%
17	Clobutinol/Orciprenaline	1660	0.23%
18	Aminophylline	1275	0.17%
19	Other	30741	4.19%

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

The top 5 remained unchanged for 2006 (refer to table 4.12). The prevalence of the first 2 active ingredients decreased slightly. Bromhexine/orciprenaline showed an increase in prevalence of 0.41% (n=117888).

Salmeterol/fluticasone prevalence increased as well from 7.56% (n=51129) in 2005 to 8.1% (n=59503) in 2006.

Table 4.13: Prevalence of bronchodilators according to active ingredient during 2007

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Theophylline/Etophylline	136018	22.61%
2	Bromhexine/Orciprenaline	101582	16.88%
3	Salbutamol	99444	16.53%
4	Salmeterol/Fluticasone	59603	9.91%
5	Theophylline	59498	9.89%
6	Ipratropium/Salbutamol	30024	4.99%
7	Budesonide/Formoterol	22726	3.78%
8	Fenoterol	20794	3.46%
9	Fenoterol/Ipratropium	17441	2.90%
10	Salmeterol	11075	1.84%
11	Ipratropium	10531	1.75%
12	Tiotropium	8481	1.41%
13	Formoterol	8411	1.40%
14	Aminophylline/Ephedrine	2735	0.46%
15	Terbutaline/Guaifenesin	1993	0.33%
16	Clobutinol/Orciprenaline	1093	0.18%
17	Other	10219	1.70%

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

In 2007 the order of the top 5 active ingredients changed (refer to table 4.13). Theophylline/etophylline was still the most frequently prescribed active ingredient, but the prevalence decreased by 2.02% from 2006 (n=180817) to 2007 (n=136018).

Bromhexine/orciprenaline moved up to second place and showed an increased prevalence of 0.83% from 2006 (n=117888) to 2007 (n=101582). This caused salbutamol to move to third place, but its prevalence still increased by 0.27%.

Salmeterol/fluticasone managed to move up a position and ended in the fourth position. Its prevalence showed an increase of 1.8%, which means that salmeterol/fluticasone usage had only been increasing during the 2005 to 2007 period.

Theophylline usage increased by 0.3% from 2006 (n=70427) to 2007 (n=59498), but it dropped a position from 2006.

Table 4.14: Prevalence of bronchodilators according to active ingredient during 2008

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Theophylline/Etophylline	114402	22.65%
2	Salbutamol	84240	16.68%
3	Bromhexine/Orciprenaline	73992	14.65%
4	Salmeterol/Fluticasone	54880	10.87%
5	Theophylline	51317	10.16%
6	Ipratropium/Salbutamol	24925	4.94%
7	Budesonide/Formoterol	24766	4.90%
8	Fenoterol	14865	2.94%
9	Fenoterol/Ipratropium	13575	2.69%
10	Salbutamol/Bromhexine	10267	2.03%
11	Formoterol	8559	1.70%
12	Ipratropium	8520	1.69%
13	Tiotropium	7563	1.50%
14	Salmeterol	6488	1.29%
16	Terbutaline/Guaifenesin	1336	0.27%
17	Aminophylline/Ephedrine	1065	0.21%
18	Aminophylline	669	0.13%
19	Terbutaline	618	0.12%
20	Other	2944	0.58%

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

There were not any changes regarding the active ingredients in the top 5 of 2008 (refer to table 4.14). Theophylline/etophylline was still in the top position, followed by salbutamol, which showed another increase in prevalence (0.16%).

Bromhexine/orciprenaline was once again ranked third and for the first time showed a decrease of 2.23% in prevalence.

Salmeterol/fluticasone usage continued to increase. In 2007 the prevalence was 9.91% (n=59603) and in 2008 it increased to 10.87% (n=54880).

Theophylline, despite being phased out by prescribers, demonstrated another increase in prevalence from 9.89% in 2007 (n=59498) to 10.61% in 2008 (n=51317) (refer to section 2.5.2.2).

Summary

There were not many changes in the top 5 prescribed bronchodilators from 2005 to 2008 (refer to tables 4.11 - 4.14). Theophylline/etophylline claimed the first position from 2005 to 2008, but overall showed a decrease in prevalence of 2.34%. This decrease had no effect on the active ingredient's position on the list of most frequently prescribed bronchodilators and was by far the most prevalent active ingredient. The negative aspect of this, however, is that this active ingredient is mostly indicated for problems with coughing, although it has bronchodilatation properties as well (Snyman, 2009a:168).

Salbutamol was the most often prescribed β_2-agonist and showed an increase of 0.11% in the prevalence from 2005 (n=112009) to 2008 (n=84240).

Bromhexine/orciprenaline, another cough mixture, proved to have become less popular and showed a decrease of 0.99% in prevalence from 2005 (n=105725) to 2008 (n=73992).

Theophylline, which is considered an older asthma drug, was still being prescribed frequently and was constantly within the top 5 positions for bronchodilators.

Salmeterol/fluticasone was the first combination on the list that contained a glucorticoid and was being prescribed more frequently every year. Its prevalence increased every year from 2005 (n=51129) to 2008 (n=54880) and overall showed an increase of 3.3%. Despite the number of medicine items decreasing in the total database from 2005 to 2008, the number of medicine items for salmeterol/fluticasone still managed to increase.

In general, combinations of active ingredients were prescribed often in the bronchodilator group.

Table 4.15: Summary of increases and decreases of broncholdilators from 2005 to 2008

Theophylline/Etophylline	↓
Salbutamol	↑
Bromhexine/Orciprenaline	↓
Theophylline	↓
Salmeterol/Fluticasone	↑
Ipratropium/Salbutamol	↑
Fenoterol	↓
Fenoterol/Ipratropium	↓
Budesonide/Formoterol	↑
Salmeterol	↓
Ipratropium	↓
Formoterol	↑
Tiotropium	↑

Aminophylline/Ephedrine	↓
Terbutaline/Guaifenesin	↓
Hexoprenaline	↓
Clobutinol/Orciprenaline	↓
Etafedrine/Ambuphylline	↓
Terbutaline	↓
Aminophylline	↓
Theophylline/Ethylenediamine	↑
Guaifenesin/Theophylline	↑
Theophylline/Ephedrine	↑

4.4.6.3.2 Anti-asthmatics

Table 4.16 indicates the most frequently prescribed anti-asthmatics (group 10.4) of 2005.

Table 4.16: Prevalence of anti-asthmatics according to active ingredient during 2005

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Budesonide	52442	41.83%
2	Montelukast	25922	20.68%
3	Beclomethasone	23688	18.89%
4	Fluticasone	14625	11.66%
5	Ketotifen	8289	6.61%
6	Zafirlukast	415	0.33%

* **%**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

Budesonide was the drug with the highest prevalence at 41.83% (n=52442) in 2005. Montelukast was ranked highest as non-glucocorticoid and had a prevalence of 20.67%. This might be due to its convenient dosage form and its safety in children (refer to section 2.5.2.3). Beclomethasone (18.89%) and fluticasone (11.66%) were the other inhaled corticosteroids that had a significant prevalence among anti-asthmatics. Ketotifen did not seem to be a very popular choice in asthma prevention and had a prevalence of 6.61%.

Table 4.17: Prevalence of anti-asthmatics according to active ingredient during 2006

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Budesonide	57731	41.25%
2	Montelukast	34850	24.90%
3	Beclomethasone	24276	17.35%
4	Fluticasone	13074	9.34%
5	Ketotifen	7963	5.69%
6	Ciclesonide	1601	1.14%
7	Zafirlukast	465	0.33%

* **%**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

In 2006 budesonide was still the most frequently prescribed anti-asthmatic (refer to table 4.17). Montelukast showed a raise in prevalence of 4.23% from 2005 (n=25922) to 2006 (n=34850). Beclomethasone and fluticasone decreased from 2005 to 2006 by 1.55% and 2.32% respectively. A new inhaled corticosteroid, ciclesonide was introduced in 2006, but was only prescribed 1601 times (1.14%). The prevalence of ketotifen decreased by 0.92%.

Table 4.18: Prevalence of anti-asthmatics according to active ingredient during 2007

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Budesonide	50040	40.40%
2	Montelukast	38807	31.33%
3	Beclomethasone	16183	13.07%
4	Fluticasone	10491	8.47%
5	Ketotifen	5308	4.29%
6	Ciclesonide	2586	2.09%
7	Zafirlukast	445	0.36%

* **%**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

In table 4.18 the most frequently prescribed active ingredients in 2007 were still in the same order as in 2005 and 2006. Budesonide was in the first position, but its prevalence still declined from 41.25% in 2006 (n=57731) to 40.4% in 2007 (n=50040). Montelukast demonstrated a large increase in prevalence of 6.43% from 2006 (n=34850) to 2007 (n=38807), despite the decreasing number of prescriptions in the total database (refer to table 4.1). The prevalence of beclomethasone and fluticasone and ketotifen decreased further, while ciclesonide showed an increase of 0.94% in prevalence from 2006 to 2007.

Table 4.19: Prevalence of anti-asthmatics according to active ingredient during 2008

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Budesonide	42229	39.78%
2	Montelukast	35308	33.26%
3	Beclomethasone	14478	13.64%
4	Fluticasone	7732	7.28%
5	Ketotifen	3493	3.29%
6	Ciclesonide	2471	2.33%
7	Zafirlukast	437	0.41%

* **%**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items for each active ingredient multiplied by 100.

According to table 4.19, 2008 did not show any changes in the order of the top anti-asthmatics. Budesonide was the most frequently prescribed drug to control asthma, but once again showed a decrease in prevalence. Montelukast had the opposite result and increased in prevalence by 1.93% from 2007 (n=38807) to 2008 (n=35308). Beclomethasone usage increased, but fluticasone and ketotifen decreased once more.

Summary

The positions of the anti-asthmatics stayed the same from 2005 to 2008 (refer to tables 4.16 – 4.19). Budesonide was the preferred anti-asthmatic to prescribe for asthma control from 2005 to 2008, although its prevalence decreased during this study period.

Montelukast was being used more regularly every year and overall its prevalence increased by 12.59%. In 2005 the prevalence of montelukast (20.68%) was almost half of that of budesonide (41.83%). By 2008 the difference between the prevalence of budesonide and the prevalence of montelukast was only 6.52%.

Beclomethasone usage decreased overall by 5.25% from 2005 (n=23688) to 2008 (n=14478). The prevalence of fluticasone, another inhaled corticosteroid, decreased by 4.38% from 2005 (n=14625) to 2008 (n=7732). Ciclesonide is the most recent inhaled corticosteroid ans its prevalence increased by 1.18% over a period of three years.

Zafirlukast was prescribed a great deal less than montelukast, the other leukotriene receptor antagonist. This may be due to its many side-effects and interactions with other drugs (refer to 2.5.2.3).

Table 4.20: Summary of increases and decreases of anti-asthmatics from 2005 to 2008

Budesonide	↓
Montelukast	↑
Beclomethasone	↓
Fluticasone	↓
Ketotifen	↓
Ciclesonide	↑
Zafirlukast	↑

4.5 Paediatric asthma

The focus of this study was on paediatric asthma and its drug treatment, therefore asthma in the age groups 0 – 4 years and >4 ≤ 11 years will be discussed in the section below.

4.5.1 The prevalence of paediatric asthma

Table 4.21: The prevalence of asthma as a percentage of the total database for age groups 0 – 4 years and >4 ≤ 11 years

		0 – 4 years			>4 ≤ 11 years		
Year		**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**
2005	**Total database**	76175	279560	694676	146334	440544	1095807
	Asthma database	29156	49006	58658	46037	77156	94403
	%Prevalence of asthma*	**38.28%**	**17.53%**	**8.44%**	**31.46%**	**17.51%**	**8.61%**
2006	**Total database**	74980	287345	726266	145048	453632	1140677
	Asthma database	30186	52380	63591	47157	82119	102001
	%Prevalence of asthma*	**40.26%**	**18.23%**	**8.76%**	**32.51%**	**18.10%**	**8.94%**
2007	**Total database**	50563	227126	579239	114219	382519	959273
	Asthma database	23349	42776	52911	36847	66521	83794
	%Prevalence of asthma*	**46.18%**	**18.83%**	**9.13%**	**32.26%**	**17.39%**	**8.74%**
2008	**Total database**	25464	111358	281110	86328	289540	712330
	Asthma database	11306	21129	26246	28347	51684	64715
	%Prevalence of asthma*	**44.40%**	**18.97%**	**9.34%**	**32.84%**	**17.85%**	**9.08%**

***** %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year and age group multiplied by 100. This is done for number of patients, prescriptions and items.

4.5.1.1 Number of patients

In table 4.21, the prevalence of paediatric asthma is indicated for very young children and older children. The number of patients in the younger age group is less than in older children according to the total and asthma database. This is, however, not an indication of the difference in prevalence between the age groups.

The 0 – 4 years age group had a very large prevalence of asthma among patients, which continued to increase from 2005 to 2008. By 2007, 46.18% of all patients between the ages of 0 and 4 years used medication according to the asthma database. Overall, the prevalence

of the number of patients using asthma medication in this age group increased by 6.12% from 2005 (n=29156) and 2008 (n=11306).

The prevalence for the number of patients was higher in the 0 – 4 year age group than in the >4 ≤ 11 years age group for the total study period. In addition, the prevalence for the older age group remained fairly constant throughout the study period and only increased by 1.38% from 2005 (n=46037) to 2008 (n=28347).

4.5.1.2 Number of prescriptions

Table 4.22: Number of prescriptions according to the total and asthma database per age group

		0 - 4 years		>4 ≤ 11 years	
Year		**Number of prescriptions**	**Number of prescriptions per patient per year**	**Number of prescriptions**	**Number of prescriptions per patient per year**
2005	**Total database**	279560	3.67 ± 3.66	440544	3.01 ± 3.01
	Asthma database	49006	1.68 ± 1.44	77156	1.68 ± 1.63
	% Prevalence of asthma*	**17.53%**		**17.51%**	
2006	**Total database**	287345	3.83 ± 3.80	453632	3.13 ± 3.12
	Asthma database	52380	1.74 ± 1.51	82119	1.74 ± 1.74
	% Prevalence of asthma*	**18.23%**		**18.10%**	
2007	**Total database**	227126	4.49 ± 4.14	382519	3.35 ± 3.33
	Asthma database	42776	1.83 ± 1.66	66521	1.81 ± 1.89
	% Prevalence of asthma*	**18.83%**		**17.39%**	
2008	**Total database**	111358	4.37 ± 4.18	289540	3.35 ± 3.44
	Asthma database	21129	1.87 ± 1.79	51684	1.82 ± 1.92
	% Prevalence of asthma*	**18.97%**		**17.85%**	

* %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year an age group multiplied by 100.

Table 4.22 indicates the number of prescriptions that were dispensed during the study period. The difference in prevalence between the two age groups according to prescriptions is not as prominent as in number of patients.

The 0 - 4 years age group's prevalence of asthma prescriptions increased every year from 2005 to 2008. By the end of 2008 18.97% (n=21129) of all prescriptions dispensed to

children 4 years and younger, were for asthma medication. In 2005 the prevalence of asthma prescriptions only differed by 0.02% between the two age groups, but this changed as the prevalence of the younger age group increased, but the prevalence of the prescriptions in older children showed increases and decreases.

Regarding the number of prescriptions per patient per year, there was a very slight difference between the age groups. There was, however, an indication that children on the total database received more prescriptions per year, than the children included in the asthma database. The average for every year indicated that children on the asthma database received between one and two prescriptions per year. According to the total database, younger children received more prescriptions per year than older children on average. Once again, if a child had chronic asthma, the average number of prescriptions that were filled for the child was an indication of non-adherence (Bester & Hammann, 2008:20).

4.5.1.3 Number of medicine items

According to table 4.23, there was an increase in the prevalence of the number of asthma medicine items that were dispensed to children between the ages of 0 and 4 years. From 2005 (n=58658) to 2008 (n=26246) there was an increase of 0.9%. The prevalence for the number of asthma medicine items in the older age group (>4 ≤ 11 years) increased by 0.47% from 2005 (n=94403) to 2008 (n=64715).

In 2005 and 2006 the prevalence for the number of medicine items was slightly higher in children aged >4 ≤ 11 years than in children 0 - 4 years. This was the only time in the study period that this occurred.

The number of medicine items that appeared on a prescription was almost identical for the two age groups during the study period. The total database indicated that an average of 2 or 3 medicine items appeared on a perscription for a child. In the asthma database the number of medicine items per prescription was on average between 1 and 2 items. The results reveal that a variety of different asthma medication was not prescribed to children at the same time.

Table 4.23: Number of medicine items and number of medicine items per prescription on the total and asthma database per age group

		0 - 4 years				>4 ≤ 11 years			
Year		**Number of medicine items**	**Number of medicine items per prescription**	**Minimum number of medicine items per prescription**	**Maximum number of medicine items per prescription**	**Number of medicine items**	**Number of medicine items per prescription**	**Minimum number of medicine items per prescription**	**Maximum number of medicine items per prescription**
2005	**Total database**	694676	2.48 ± 1.34	1	15	1095807	2.49 ± 1.34	1	17
	Asthma database	58658	1.20 ± 0.47	1	6	94403	1.22 ± 0.49	1	6
	%Prevalence of asthma*	**8.44%**				**8.61%**			
2006	**Total database**	726266	2.53 ± 1.37	1	15	1140677	2.51 ± 1.36	1	18
	Asthma database	63591	1.21 ± 0.50	1	8	102001	1.24 ± 0.51	1	7
	%Prevalence of asthma*	**8.76%**				**8.94%**			
2007	**Total database**	579239	2.55 ± 1.39	1	16	959273	2.51 ± 1.37	1	14
	Asthma database	52911	1.24 ± 0.52	1	5	83794	1.26 ± 0.53	1	6
	%Prevalence of asthma*	**9.13%**				**8.74%**			
2008	**Total database**	281110	2.52 ± 1.38	1	18	712330	2.46 ± 1.37	1	15
	Asthma database	26246	1.24 ± 0.52	1	5	64715	1.25 ± 0.53	1	6
	%Prevalence of asthma*	**9.34%**				**9.08%**			

***** %Prevalence of asthma is calculated by dividing the asthma database by the total database for the specific year and age group multiplied by 100.

4.5.2 Cost of paediatric asthma medicine treatment

Table 4.24: The cost of asthma in different age groups as a percentage of the total database

Age group	Year	Total expenditure (R)	Asthma expenditure (R)	% Asthma expenditure*
0 – 4 years	**2005**	37 079 768.54	4 314 111.19	11.63%
	2006	38 293 700.98	4 821 121.46	12.59%
	2007	31 687 674.78	4 442 393.70	14.02%
	2008	16 239 122.71	2 551 088.01	15.71%
>4 ≤ 11 years	**2005**	64 294 783.96	8 066 097.29	12.55%
	2006	66 659 219.21	8 763 940.59	13.15%
	2007	49 798 273.45	7 949 374.33	15.96%
	2008	40 722 913.39	6 821 627.93	16.75%

* %Asthma expenditure is calculated by dividing the asthma expenditure by the total expenditure for the specific year and age group multiplied by 100.

The percentage that asthma costs represent as part of the total database (table 4.24) is much higher in the paediatric age groups than in the total asthma population (refer to table 4.3). The paediatric age groups also showed a steady increase in the percentage of asthma expenditure, where the total asthma population showed a decrease (refer to table 4.3).

The older paediatric age group had a higher asthma expenditure than the younger group, which means that children between the ages of >4 ≤ 11 years need more asthma medication.

In both age groups, asthma expenditure as part of the total database was the lowest in 2005 and the highest in 2008. The largest increase was from 2006 to 2007.

The asthma expenditure in this study was only concerned with the cost of medication used to treat asthma. Hospitalisation and other tangible costs, that play an important role in the overall costs of asthma, were not included (refer to section 2.7.3).

4.5.3 Paediatric asthma prevalence according to gender

Table 4.25 provides information regarding the prevalence of paediatric asthma according to gender. The general trend seen is that male paediatric asthma is more prevalent than female paediatric asthma. This correlates with the literature, which states that asthma has a higher prevalence in boys before puberty (Postma, 2007:S133, S141). Female asthma becomes more prevalent after the age of 12 years (Wjst & Boakye, 2007:203).

Table 4.25: Prevalence of paediatric asthma according to gender

			0 – 4 years			>4 ≤ 11 years			> 11 years		
Year	**Gender**		**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**
2005	**Female**	**Total database**	36785	132610	327836	70537	209266	524155	735064	4694618	10898199
		Asthma database	13501	22171	26251	21488	34880	42189	152929	291471	363420
		%Prevalence of asthma*	**36.70%**	**16.72%**	**8.01%**	**30.46%**	**16.67%**	**8.05%**	**20.80%**	**6.21%**	**3.33%**
	Male	**Total database**	39368	146856	366655	75561	230676	570090	550576	2970687	6797716
		Asthma database	15647	26824	32396	24481	42175	52080	118897	225982	284133
		%Prevalence of asthma*	**39.75%**	**18.27%**	**8.84%**	**32.40%**	**18.28%**	**9.14%**	**21.60%**	**7.61%**	**4.18%**
2006	**Female**	**Total database**	36317	136923	346205	70169	214484	543265	762405	4984795	11810237
		Asthma database	14133	23942	28944	22062	36986	45219	166750	319645	399382
		%Prevalence of asthma*	**38.92%**	**17.49%**	**8.36%**	**31.44%**	**17.24%**	**8.32%**	**21.87%**	**6.41%**	**3.38%**
	Male	**Total database**	38645	150349	379898	74756	238871	596767	574690	3176108	7426493
		Asthma database	16046	28428	34637	25066	45101	56746	127983	244967	308758
		%Prevalence of asthma*	**41.52%**	**18.91%**	**9.12%**	**33.53%**	**18.88%**	**9.51%**	**22.27%**	**7.71%**	**4.16%**

Table 4.25 (continued): Prevalence of paediatric asthma according to gender

			0 – 4 years			>4 ≤ 11 years			> 11 years		
Year	**Gender**		**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**	**Number of patients**	**Number of prescriptions**	**Number of medicine items**
2007	**Female**	**Total database**	23344	107169	273054	55267	181332	459687	574747	4466410	10776605
		Asthma database	10854	19455	23946	17364	30191	37571	132273	264693	332952
		%Prevalence of asthma*	**44.60%**	**18.15%**	**8.77%**	**31.42%**	**16.65%**	**8.17%**	**23.01%**	**5.93%**	**3.09%**
	Male	**Total database**	26229	119957	306185	58923	201134	499475	438689	2833264	6756806
		Asthma database	12495	23321	28965	19477	36323	46215	101392	202395	332952
		%Prevalence of asthma*	**47.64%**	**19.44%**	**9.46%**	**33.06%**	**18.06%**	**9.25%**	**23.11%%**	**7.14%**	**4.93%**
2008	**Female**	**Total database**	12324	52971	133500	41759	136748	339874	484171	3872666	9420554
		Asthma database	5426	9905	12138	13236	23188	28797	113000	232468	292725
		%Prevalence of asthma*	**44.03%**	**18.70%%**	**9.09%**	**31.70%**	**16.69%**	**8.47%**	**23.34%**	**6.00%**	**3.11%**
	Male	**Total database**	13140	58387	147610	44569	152792	372456	378534	2502299	6025259
		Asthma database	5880	11224	14108	15111	28496	35918	88201	179701	227453
		%Prevalence of asthma*	**44.75%**	**19.22%**	**9.56%**	**33.90%**	**18.65%**	**9.64%**	**23.30%**	**7.18%**	**3.77%**

* %Prevalence of asthma is calculated by dividing the asthma database by the total database and multiplying by 100.

The definite trend that can be observed from table 4.25 is that there is still a very small difference between the age groups as also seen in table 4.21.

Female patients in the age group 0 – 4 years showed an increase in prevalence from 2005 (n=13501) to 2008 (n=5426) of 7.33% on the asthma database. Male patients showed an increase of 5% only from 2005 (n=15647) to 2008 (n=5880), but the prevalence was 0.72% higher than in females. The number of asthma patients' prevalence was the only category in which the age groups did show a difference. The prevalence was much lower in the >4 ≤ 11 years age group in females and males, with a prevalence in 2008 of 31.70% (n=13236) and 33.90% (n=15111) respectively, although the number of patients was higher than in the 0 – 4 years age group.

Male asthma prescriptions were more prevalent than female asthma prescriptions. There were once again only minor differences between the two age groups. In the 0 – 4 years age group, the prevalence of the number of prescriptions in females increased by 1.98% from 2005 (n=22171) to 2008 (n=9905), despite a decrease in the number of prescriptions on the total database. Males in this age group showed a higher prescription prevalence, but an increase of only 0.95% from 2005 (n=26824) to 2008 (n=11224). The >4 ≤ 11 years age group showed a similar trend, with the male prevalence higher than the female prevalence. In this case, however, male and female prevalence increased with 0.37% and 0.29% respectively from 2005 to 2008.

Regarding asthma medicine items, male patients received more items than female patients in both age groups. Both genders, however, showed a steady increase in prevalence. In the 0 – 4 years age group, male prevalence for number of medicine items on the asthma database increased by 0.72% from 2005 (n=32396) to 2008 (n=14108), while in females it increased by 1.08% from 2005 (n= 26251) to 2008 (n=14108). The increase in prevalence did not differ very much in the >4 ≤ 11 years age group. In males the prevalence increased by 0.5% from 2005 (n=52080) to 2008 (n=35918) and in females it increased by 0.42% from 2005 (n=42189) to 2008 (n=28797).

The prevalence of asthma in patients older than 11 years is supposed to be higher in females than in males (refer to section 2.6.5). This is not the case according to table 4.25, because the prevalence was higher in males throughout the study period.

4.5.4 Paediatric asthma prevalence according to type of prescriber

Paediatric asthma medicine can be prescribed by different types of prescribers. Firstly, there are general practitioners that are consulted by all patients and do not specialise in any type of disease. Paediatricians specialise in the treatment of children and pulmonologists specialise in pulmonary diseases. Other specialists are also entitled to prescribe asthma medication, but they are not specified in this study.

Table 4.26: The prevalence of paediatric asthma prescriptions according to type of prescriber in 2005

Prescriber	0 - 4 years		> 4 ≤ 11 years	
	%Prevalence*	Number of prescriptions (n)	%Prevalence*	Number of prescriptions (n)
General practitioner	59.63%	29224	71.07%	54836
Other specialists	13.09%	6413	13.36%	10308
Paediatrician	27.26%	13359	15.45%	11920
Pulmonologist	0.02%	10	0.12%	92
Total number of prescriptions (N)		49006		77156

* %Prevalence is calculated by dividing the number of prescriptions (n) by the total number of prescriptions (N) for each prescriber in each age group multiplied by 100.

The trends seen in table 4.26 displayed the prescribers that patients consulted to get their asthma medication. Most patients under the age of 4 years are seen by a general practitioner (59.63%). The specialists have a lower prevalence when it comes to prescribing asthma medication. Paediatricians have the second highest prevalence among the younger age group at 27.26% (n=13359). The prevalence of paediatricians is 11.81% higher in age group 0 - 4 years than > 4 ≤ 11 years. This can be expected, because children 0 – 4 years are referred to a specialist when the child reaches Step 3 care, in comparison to older children that are referred only when Step 4 care is needed (refer to section 2.6.6). Therefore, the general practitioners also have a higher prevalence in the > 4 ≤ 11 years age group (71.07%). Other specialists contributed 13.09% (n=6413) and 13.36% (n=10308) to the 0 - 4 years and > 4 ≤ 11 years age groups respectively. Pulmonologists have a very low prevalence among the issuing of paediatric asthma prescriptions. Parents with asthmatic children would therefore rather go to their general practitioner or a paediatrician and then may be referred to a pulmonologist. There are also fewer pulmonologists than paediatricians and it has to be considered that there are more general practitioners than specialists in South Africa (Department of Labour, 2008:10).

Table 4.27: The prevalence of paediatric asthma prescriptions according to type of prescriber in 2006

Prescriber	0 - 4 years		> 4 ≤ 11 years	
	%Prevalence*	Number of prescriptions (n)	%Prevalence*	Number of prescriptions (n)
General practitioner	58.84%	30819	69.65%	57199
Other specialists	12.94%	6778	13.84%	11364
Paediatrician	28.21%	14778	16.37%	13441
Pulmonologist	0.01%	5	0.14%	115
Total number of prescriptions (N)		52380		82119

* %Prevalence is calculated by dividing the number of prescriptions (n) by the total number of prescriptions (N) for each prescriber in each age group multiplied by 100.

In 2006, there was a similar pattern with regard to the prevalence of the number of prescriptions written by general practitioners and specialists (refer to table 4.27). General practitioners' prevalence decreased in both age groups. In children aged 0 – 4 years it decreased by 0.79% and in > 4 ≤ 11 years by 1.42%. The prevalence of paediatrician prescriptions on the other hand, showed an increase of 0.95% and 0.92% in age groups 0 - 4 years and > 4 ≤ 11 years respectively. Other specialists' prevalence decreased in the younger age group by 0.15%, but showed an increase in the > 4 ≤ 11 years age group of 0.48%. Pulmonologists were still not used often to write asthma prescriptions for children, and in 2006 only 5 prescriptions were written for asthma medication to children younger than 4 years in this section of the private health care sector.

Table 4.28: The prevalence of paediatric asthma prescriptions according to type of prescriber in 2007

Prescriber	0 - 4 years		> 4 ≤ 11 years	
	%Prevalence*	Number of prescriptions (n)	%Prevalence*	Number of prescriptions (n)
General practitioner	57.63%	24653	68.18%	45353
Other specialists	12.96%	5542	14.40%	9578
Paediatrician	29.38%	12567	17.27%	11487
Pulmonologist	0.03%	14	0.15%	103
Total number of prescriptions (N)		42776		66521

* **%**Prevalence is calculated by dividing the number of prescriptions (n) by the total number of prescriptions (N) for each prescriber in each age group multiplied by 100.

Table 4.28 displays the prevalence of the asthma prescriptions by the different types of prescribers in 2007. General practitioners once again showed a decrease in prevalence in both age groups. In the 0 - 4 years age group, general practitioners contributed 1.21% less to the total number of prescriptions on the asthma database than in 2006. The > 4 ≤ 11 years age group showed a decrease of 1.47%. Paediatricians showed the same pattern as in 2006, with an increase in both age groups, but the prevalence in the younger age group was still higher. Pulmonologists were still not consulted very often by paediatric patients.

Table 4.29: The prevalence of paediatric asthma prescriptions according to type of prescriber in 2008

Prescriber	0 - 4 years		> 4 ≤ 11 years	
	%Prevalence*	Number of prescriptions (n)	%Prevalence*	Number of prescriptions (n)
General practitioner	58.50%	12360	66.94%	34599
Other specialists	13.85%	2927	15.10%	7802
Paediatrician	27.59%	5829	17.80%	9201
Pulmonologist	0.06%	13	0.16%	82
Total number of prescriptions (N)		21129		51684

* **%**Prevalence is calculated by dividing the number of prescriptions (n) by the total number of prescriptions (N) for each prescriber in each age group multiplied by 100.

Table 4.29 displays the prevalence of prescriptions with asthma medication by different prescribers in 2008. In the 0 - 4 years age group the prevalence for general practitioners increased for the first time during the study period. An increase of 0.87% was seen. In the > 4 ≤ 11 years age group, however, the prevalence of general practitioners still decreased with 1.24% in 2008. Other specialists were used more often to prescribe asthma medication in both age groups in 2008. Paediatrician prescriptions' prevalence also showed a different trend. In the 0 – 4 years age group, the prevalence decreased with 1.79%. This is the first time that this occurred during the study period. At the same time, the paediatrician prevalence increased slightly (0.53%) in the > 4 ≤ 11 years age group. Pulmonologists still did not play a significant role in the prescribing patterns of paediatric asthma medication.

Summary

The general trend seen in the prescribing patterns of the different prescribers is that general practitioners are becoming less involved in the treatment if paediatric asthma and the prevalence of their prescriptions decreased from 2005 to 2008 and more parents would rather take their child to a paediatrician for asthma medication prescriptions.

In the 0 - 4 years age group general practitioners are consulted the most often, but paediatricians also have a presence among the prescribers (refer to tables 4.26 – 4.29). Pulmonologists have the lowest prevalence of all the prescribers that are involved in the prescribing of asthma medication to young children.

In the older age group, > 4 ≤ 11 years, the same trend as in the younger age group was displayed with regard to the general practitioners and paediatricians. The prevalence of the general practitioners in the > 4 ≤ 11 years age group was, however higher than in the 0 - 4 years age group.

There was not sufficient information regarding the other specialists that appeared on the database and it was not clear what kind of practitioners had been involved.

Table 4.30: Summary of increases and decreases of prevalence of prescriptions per type of prescriber from 2005 to 2008

0 - 4 years	
General practitioner	↓
Other specialists	↑
Paediatrician	↑
Pulmonologist	↑

> 4 ≤ 11 years	
General practitioner	↓
Other specialists	↑
Paediatrician	↑
Pulmonologist	↑

4.5.4.1 Type of prescriber and number of items

0 – 4 years of age

Table 4.31 displays the trends seen in the 0 – 4 years age group with regard to the number of items the different prescribers wrote on prescriptions during the study period. Pulmonologists prescribed the largest number of items per prescription on average from 2005 to 2008, but they also prescribed the lowest number of items of all the prescribers. Paediatricians' and general practitioners' number of items per prescription showed a steady increase from 2005 to 2008. Paediatricians averaged between 1 or 2 items per prescription from 2005 to 2008. General practitioners were most often consulted and prescribed the most items, but had a lower average of number of items per prescription than paediatricians. Other specialists had the lowest average and this remained constant over the four-year study period. When it came to the maximum number of items per prescription, general practitioners had the highest number and pulmonologists the lowest number every year. Prescribers and the number of items they prescribed for a paediatric patient did not show a noteworthy difference in this age group.

Table 4.31: Number of medicine items and number of medicine items per prescription on the asthma database per prescriber in the 0 – 4 years age group

Year		General practitioner	Other specialists	Paediatrician	Pulmonologist
2005	Number of medicine items	34345	6893	17404	16
	Number of medicine items per prescription	1.18 ± 0.45	1.07 ± 0.30	1.30 ± 0.56	1.60 ± 0.52
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	6	5	5	2
2006	Number of medicine items	36589	7303	19691	8
	Number of medicine items per prescription	1.19 ± 0.47	1.08 ± 0.29	1.33 ± 0.59	1.60 ± 0.55
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	8	5	6	2
2007	Number of medicine items	29754	5997	17127	33
	Number of medicine items per prescription	1.21 ± 0.48	1.08 ± 0.31	1.36 ± 0.62	2.36 ± 0.74
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	5	5	5	3
2008	Number of medicine items	15065	3134	8024	23
	Number of medicine items per prescription	1.22 ± 0.49	1.07 ± 0.28	1.38 ± 0.63	1.77 ± 0.83
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	5	4	5	3

> 4 ≤ 11 years of age

Table 4.32 demonstrates the difference in prescribing patterns of the different prescribers in the > 4 ≤ 11 years age group. Once again pulmonologists had the highest average number of items per prescription, followed by paediatricians and general practitioners.

Table 4.32: Number of medicine items and number of medicine items per prescription on the asthma database per prescriber in the > 4 ≤ 11 years age group

Year		General practitioner	Other specialists	Paediatrician	Pulmonologist
2005	Number of medicine items	66402	11277	16575	149
	Number of medicine items per prescription	1.21 ± 0.48	1.09 ± 0.32	1.39 ± 0.60	1.62 ± 0.78
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	6	4	5	4
2006	Number of medicine items	70314	12447	19071	169
	Number of medicine items per prescription	1.23 ± 0.50	1.10 ± 0.33	1.42 ± 0.62	1.47 ± 0.64
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	7	4	6	3
2007	Number of medicine items	56513	10505	16598	178
	Number of medicine items per prescription	1.25 ± 0.52	1.10 ± 0.34	1.44 ± 0.65	1.73 ± 0.77
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	6	6	5	5
2008	Number of medicine items	42881	8574	13121	139
	Number of medicine items per prescription	1.24 ± 0.51	1.10 ± 0.35	1.43 ± 0.65	1.70 ± 0.64
	Minimum number of medicine items per prescription	1	1	1	1
	Maximum number of medicine items per prescription	5	5	6	3

This ranking is the same as in the 0 – 4 years age group. A difference in the two groups can be seen in paediatrician prescribing patterns, which were slightly higher in this age group. The average number of items per prescription for all the prescribers remained fairly constant from 2005 to 2008. The differences in the number of medicine items per prescription were, however, not significant. The maximum number of items per prescription varied from 3 to 7

among the different prescribers. General practitioners once again prescribed the highest number of items per prescription, but in the case of this age group paediatricians also played a role in prescribing a larger number of items per prescription.

4.5.4.2 Type of prescriber and cost

0 – 4 years of age

In table 4.33 evidence of the costs of prescriptions written by the different prescribers on the asthma database can be seen.

Pulmonologists had the highest average cost per prescription, although they wrote the least prescriptions during the study period. Although paediatricians did not write most of the prescriptions to this age group, their total cost was the largest. On average, their prescriptions were more expensive than those of the general practitioners and other health specialists from 2005 to 2008. The average cost per prescriptions written by paediatricians only increased.

When comparing this to table 4.31 and the number of items that were prescribed by the different prescribers, it can be concluded that paediatricians tend to write more expensive prescriptions than general practitioners (*d*-value of 0.65 in 2008). The difference in the costs of these prescriptions are, however, not as significant as the difference in the cost of the prescriptions between general practitioners and pulmonologists (*d*-value of 1.23 in 2008). Pulmonologists also wrote more expensive prescriptions than paediatricians (*d*-value of 0.85 in 2008). Therefore, it could be concluded that in the 0 – 4 years age group pulmonologist wrote the most expensive prescriptions, followed by paediatricians and then general practitioners.

The average cost per prescription for all the prescribers, except pulmonologists, showed an increase from 2005 to 2008. A sharp increase occurred from 2007 to 2008 in paediatricians and general practitioners, despite the total cost that was declining.

Table 4.33: The costs of prescriptions on the asthma database per prescriber in the 0 – 4 years age group

Year		General practitioner	Other specialists	Paediatrician	Pulmonologist
2005	**Number of prescriptions**	29224	6413	13359	10
	Average cost per prescription(R)	64.39 ± 105.22	59.68 ± 99.88	153.17 ± 154.35	328.21 ± 278.32
	Total cost (R)	1 881 854.02	382 726.75	2 046 248.32	3 282.10
2006	**Number of prescriptions**	30819	6778	14778	5
	Average cost per prescription(R)	67.22 ± 111.08	56.03 ± 96.30	160.10 ± 160.77	766.74 ± 516.30
	Total cost (R)	2 071 550.92	379 766.18	2 365 970.68	3 833.68
2007	**Number of prescriptions**	24653	5542	12567	14
	Average cost per prescription(R)	76.91 ± 122.07	55.79 ± 102.66	177.42 ± 172.71	538.70 ± 391.55
	Total cost (R)	1 895 974.28	309 185.85	2 229 691.76	7 541.81
2008	**Number of prescriptions**	12360	2927	5829	13
	Average cost per prescription(R)	92.16 ± 137.66	58.05 ± 102.40	212.00 ± 185.28	484.24 ± 319.11
	Total cost (R)	1 139 133.81	169 898.00	1 235 761.03	6 295.17

> 4 ≤ 11 years of age

The same trends that can be seen in the younger age group were also observed in the > 4 ≤ 11 years age group in table 4.34. The average cost per prescription was, however, higher in this age group.

Once again it can be said that paediatricians were responsible for more expensive prescriptions than general practitioners, but in this age group, > 4 ≤ 11 years of age, the difference in costs were more significant (*d*-value of 0.79 in 2008). Paediatricians and pulmonologists' prescriptions showed a less significant difference in cost (*d*-value of 0.51 in 2008), but the difference in cost between general practitioners and pulmonologists showed a large significance (*d*-value of 1.22 in 2008). When referring to table 4.32, the average number of items per prescription prescribed by pulmonologists appeared to be low and the average cost of a prescription (table 4.34) was the highest, when considering the number of prescriptions they wrote in total.

Therefore, it can be seen that children in the older age group were written more expensive prescriptions by general practitioners and paediatricians and that the average cost per prescription only increased from 2005 to 2008.

Table 4.34: The costs of prescriptions on the asthma database per prescriber in the > 4 ≤ 11 years age group

Year		General practitioner	Other specialists	Paediatrician	Pulmonologist
2005	Number of prescriptions	54836	10308	11920	92
	Average cost per prescription(R)	84.52 ± 127.78	68.68 ± 107.43	225.58 ± 178.39	377.24 ± 163.16
	Total cost (R)	4 634 466.39	707 970.03	2 688 955.02	34 705.85
2006	Number of prescriptions	57199	11364	13441	115
	Average cost per prescription(R)	87.24 ± 130.54	66.84 ± 105.44	221.31 ± 177.34	346.32 ± 222.98
	Total cost (R)	4 989 955.94	759 557.08	2 974 600.21	39 827.36
2007	Number of prescriptions	45353	9578	11487	103
	Average cost per prescription(R)	99.21 ± 142.86	72.40 ± 117.34	236.54 ± 184.79	381.80 ± 223.64
	Total cost (R)	4 499 492.25	693 443.66	2 717 112.59	39 325.83
2008	Number of prescriptions	34599	7802	9201	82
	Average cost per prescription(R)	109.08 ± 150.87	80.24 ± 129.54	259.92 ± 191.73	367.68 ± 211.19
	Total cost (R)	3 773 954.25	626 033.32	2 391 490.99	30 149.37

4.5.5 Paediatric asthma prevalence according to geographical area

Table 4.35 represents the prevalence of asthma patients in the nine provinces of South Africa in 2005. Although Gauteng had the most patients that claimed asthma medication in both age groups, this province did not have the highest prevalence of asthma patients. In the 0 – 4 years age group Limpopo had the highest prevalence for 2005 (36.01%), followed by Mpumalanga (35.28%) and North West (33.74%). The Western Cape had the lowest prevalence of all the provinces (25.42%). The prevalence of asthma patients in all the provinces was higher in the 0 – 4 years age group than the > 4 ≤ 11 years age group, except for the Northern Cape, that had the highest prevalence of asthma patients in the > 4 ≤ 11

years age group (31.04%). This was followed by Limpopo (30.05%) and Mpumalanga (29.14%). In this age group the Eastern Cape showed the lowest prevalence of 23.67%.

In 2006 the prevalence of asthma patients in the 0 – 4 years age group increased from 2005 in every province except the Western Cape (refer to table 4.36). This province also had the lowest prevalence in this age group (24.79%). Limpopo once again, showed the highest prevalence and an increase of 1.75% from 2005. Mpumalanga (35.64%) and North West (36.61%) were amongst the top three provinces with the highest prevalences of asthma patients again. The same pattern could be seen in the > 4 ≤ 11 years age group. The prevalence of asthma in this age group was lower and five out of the nine provinces showed an increase in prevalence from 2005 to 2006. In 2006 the provinces with the highest and lowest prevalences were the same for both age groups.

Table 4.35: Prevalence of asthma patients according to province in both age groups in 2005

		Eastern Cape	Free State	Gauteng	Kwazulu Natal	Limpopo	Mpumalanga	North West	Northern Cape	Western Cape
0 - 4 years	Total patients	7184	3512	36735	13231	6828	5535	5475	1445	12093
	Asthma patients	1935	1013	12101	3878	2459	1953	1847	436	3074
	%Prevalence of asthma*	**26.93%**	**28.84%**	**32.94%**	**29.31%**	**36.01%**	**35.28%**	**33.74%**	**30.17%**	**25.42%**
>4 ≤11 years	Total patients	12439	5776	59531	27260	16382	10840	10857	2516	17819
	Asthma patients	2944	1569	17165	7136	4923	3159	3138	781	4381
	%Prevalence of asthma*	**23.67%**	**27.16%**	**28.83%**	**26.18%**	**30.05%**	**29.14%**	**28.90%**	**31.04%**	**24.59%**

***** %Prevalence is calculated by dividing the number of asthma patients by the total number of patients in each province and age group multiplied by 100.

Table 4.36: Prevalence of asthma patients according to province in both age groups in 2006

		Eastern Cape	Free State	Gauteng	Kwazulu Natal	Limpopo	Mpumalanga	North West	Northern Cape	Western Cape
0 - 4 years	Total patients	5921	3317	37669	12789	6652	6454	5966	1377	13122
	Asthma patients	1854	1024	12660	3888	2512	2300	2184	416	3253
	%Prevalence of asthma*	**31.31%**	**30.87%**	**33.61%**	**30.40%**	**37.76%**	**35.64%**	**36.61%**	**30.21%**	**24.79%**
>4 ≤11 years	Total patients	10558	5866	61330	25804	16237	11590	12118	2470	19261
	Asthma patients	2782	1700	18128	6693	5328	3265	3697	692	4679
	%Prevalence of asthma*	**26.35%**	**28.98%**	**29.56%**	**25.94%**	**32.81%**	**28.17%**	**30.51%**	**28.02%**	**24.29%**

* **%**Prevalence is calculated by dividing the number of asthma patients by the total number of patients in each province and age group multiplied by 100.

Table 4.37 shows the prevalence of asthma patients according to province in 2007. In the 0 – 4 years age group Mpumalanga showed the highest and the Western Cape the lowest prevalence of asthma patients. Mpumalanga's prevalence indicated an increase of 3.28% from 2006 to 2007 to bring it to 38.92%. Limpopo (37.59%) and North West (37.48%) followed, but only North West was among the provinces that showed an increase in prevalence (0.87%). The older age group (> 4 ≤ 11 years) once again had a lower prevalence of asthma patients than in the 0 – 4 years age group. This was applicable to all the provinces. North West province had the highest prevalence (29.95%), followed by Limpopo (28.93%) and Gauteng (28.00%). The Western Cape had the lowest prevalence once more in this age group (24.97%).

When referring to table 4.38 it can be seen that asthma was more prevalent among the 0 – 4 years age group in 2008. The prevalence, however, decreased from 2007 to 2008 in six provinces. Mpumalanga had the highest prevalence (36.39%) and the Western Cape the lowest (27.10%). The Free State had the second highest prevalence in this age group in 2008 (36.33%). In the > 4 ≤ 11 years age group the Northern Cape had the highest prevalence for 2008 (30.43%), followed by Limpopo (29.56%) and the Free State (29.25%).

Table 4.37: Prevalence of asthma patients according to province in both age groups in 2007

		Eastern Cape	Free State	Gauteng	Kwazulu Natal	Limpopo	Mpumalanga	North West	Northern Cape	Western Cape
0 - 4 years	Total patients	3638	2244	27951	9649	4663	4797	4362	866	8524
	Asthma patients	1227	808	10243	3048	1753	1867	1635	259	2459
	%Prevalence of asthma*	**33.73%**	**36.01%**	**36.65%**	**31.59%**	**37.59%**	**38.92%**	**37.48%**	**29.91%**	**28.85%**
>4 ≤11 years	Total patients	7669	4534	50880	21798	12494	9569	9771	1908	14919
	Asthma patients	2112	1266	14246	5652	3615	2674	2926	528	3725
	%Prevalence of asthma*	**27.54%**	**27.92%**	**28.00%**	**25.93%**	**28.93%**	**27.94%**	**29.95%**	**27.67%**	**24.97%**

* %Prevalence is calculated by dividing the number of asthma patients by the total number of patients in each province and age group multiplied by 100.

Table 4.38: Prevalence of asthma patients according to province in both age groups in 2008

		Eastern Cape	Free State	Gauteng	Kwazulu Natal	Limpopo	Mpumalanga	North West	Northern Cape	Western Cape
0 - 4 years	Total patients	1796	1200	14450	4933	2128	2355	2027	418	4247
	Asthma patients	631	436	5146	1467	753	857	702	147	1151
	%Prevalence of asthma*	**35.13%**	**36.33%**	**35.61%**	**29.74%**	**35.39%**	**36.39%**	**34.63%**	**35.17%**	**27.10%**
>4 ≤11 years	Total patients	6175	3662	39734	16681	8593	7191	7013	1387	11651
	Asthma patients	1706	1071	11288	4416	2540	1924	2025	422	2901
	%Prevalence of asthma*	**27.63%**	**29.25%**	**28.41%**	**26.47%**	**29.56%**	**26.76%**	**28.87%**	**30.43%**	**24.90%**

* %Prevalence is calculated by dividing the number of asthma patients by the total number of patients in each province and age group multiplied by 100.

Summary

Table 4.39 reveals that the prevalence of asthma in the different provinces of South Africa has been decreasing more in the >4 ≤11 years age group during the study period. The prevalence from 2005 to 2008 decreased in five provinces among the >4 ≤11 years age group, while only one province showed a decrease in the 0 – 4 years age group.

Table 4.39: Summary of increases and decreases of prevalence of asthma patients in the 9 provinces of South Africa from 2005 to 2008

0 – 4 years	
Eastern Cape	↑
Free State	↑
Gauteng	↑
Kwazulu Natal	↑
Limpopo	↓
Mpumalanga	↑
North West	↑
Northern Cape	↑
Western Cape	↑

>4 ≤11 years	
Eastern Cape	↑
Free State	↑
Gauteng	↓
Kwazulu Natal	↑
Limpopo	↓
Mpumalanga	↓
North West	↓
Northern Cape	↓
Western Cape	↑

Asthma prevalence among children differed between the provinces. Limpopo, North West, Free State, Mpumalanga and the Northern Cape were always among the provinces with the highest prevalence of paediatric asthma patients. Kwazulu Natal, the Western and Eastern Cape showed a lower prevalence of asthma patients than the other provinces. This may be due to the fact that these provinces have coastlines. Rainfall does not have an important influence on the prevalence of paediatric asthma, since the Western Cape has the lowest prevalence, but is also the province with the second lowest mean annual precipitation (Breedlove & Jordaan, 2001). Urbanisation may still play a part in the prevalence of asthma, since Gauteng also had one of the higher prevalences among the provinces.

The mining industry and the location of mines in South Africa appear to have an influence on the prevalence of asthma (InfoMine, 2010). The provinces without mines, namely the Western Cape, Kwazulu Natal and the Eastern Cape have a lower prevalence than the other provinces, all of which have many mines and cities around mines.

4.5.6 Paediatric asthma prevalence according to types of medication

4.5.6.1 Bronchodilators versus anti-asthmatics

0 – 4 years of age

Table 4.40 indicated the ratio at which bronchodilators and anti-asthmatics were dispensed to the youngest age group. The case with the total number of dispensed asthma items seen in table 4.8 was that bronchodilators had a much higher prevalence than the anti-asthmatics. The same pattern was seen in the asthma items that were dispensed to children aged 0 – 4 years. However, there was a difference between the prevalence of the bronchodilators dispensed to the total asthma population and to the paediatric population. The prevalence of bronchodilators was higher than 80% for the study period in the total asthma population, whilst it only ranged from 69.34% - 78.1% in children. As it was expected the anti-asthmatics would also show a difference between the two populations. The total population showed a range of 15% to 17% for the anti-asthmatics, whereas the paediatric group a range between 21.9% and 30.66%. Another good sign is that the prevalence of bronchodilators decreased and anti-asthmatics increased during the study period (refer to table 4.40). Bronchodilators decreased by 8.76% from 2005 (n= 45810) to 2008 (n=18199) and anti-asthmatics increased by 8.76% from 2005 (n=12848) to 2008 (n=8047). These trends are following the ideal, that asthmatics patients should rather use more anti-asthmatics and rely on bronchodilators only when it is necessary. What could be troublesome, however, is that many cough mixtures are included in the bronchodilator group and patients are not necessarily asthmatic, whereas the anti-asthmatic medication is used almost exclusively for asthma patients. Since more anti-asthmatics have been dispensed over the years, more patients are therefore becoming asthmatic.

Table 4.40: The ratio of bronchodilator to anti-asthmatic medication usage in children aged 0 – 4 years

Year	Number of medicine items (N)	% Bronchodilators*	% Anti-asthmatics**	Ratio of bronchodilators to anti-asthmatics***
2005	58658	**78.1%** (n=45810)	**21.9%** (n=12848)	**3.57 : 1**
2006	63591	**75.97%** (n=48312)	**24.03%** (n=15279)	**3.16 : 1**
2007	52911	**71.63%** (n=37902)	**28.37%** (n=15009)	**2.53 : 1**
2008	26246	**69.34%** (n=18199)	**30.66%** (n=8047)	**2.26 : 1**

***** %Bronchodilators is calculated by dividing the number of bronchodilator items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

***** * %Anti-asthmatics is calculated by dividing the number of anti-asthmatic items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

*** Ratio of bronchodilators to anti-asthmatics is calculated by dividing the (n) of bronchodilators by the (n) of anti-asthmatics.

> 4 ≤ 11 years of age

The same trends can be seen in the older paediatric age group (> 4 ≤ 11 years) as in the 0 – 4 years age group (refer to table 4.40 and 4.41). The bronchodilators were still more often dispensed than the anti-asthmatics. The only difference was that the bronchodilators decreased and the anti-asthmatics decreased with less than in the 0 – 4 years age group. The bronchodilators decreased by 5.92% from 2005 (n=74542) to 2008 (n=47268). The anti-asthmatics increased by 5.92% from 2005 (n=19861) to 2008 (n=17447).

Table 4.41: The ratio of bronchodilator to anti-asthmatic medication usage in children aged >4 ≤11 years

Year	Number of medicine items (N)	% Bronchodilators*	% Anti-asthmatics**	Ratio of bronchodilators to anti-asthmatics***
2005	94403	**78.96%** (n=74542)	**21.04%** (n=19861)	**3.75 : 1**
2006	102001	**77.74%** (n=79291)	**22.26%** (n=22710)	**3.49 : 1**
2007	83794	**74.85%** (n=62718)	**25.15%** (n=21076)	**2.98 : 1**
2008	64715	**73.04%** (n=47268)	**26.96%** (n=17447)	**2.71 : 1**

***** %Bronchodilators is calculated by dividing the number of bronchodilator items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

***** * %Anti-asthmatics is calculated by dividing the number of anti-asthmatic items dispensed (n) by the total number of asthma items dispensed (N) for the specific year multiplied by 100.

*** Ratio of bronchodilators to anti-asthmatics is calculated by dividing the (n) of bronchodilators by the (n) of anti-asthmatics.

4.5.6.2 Therapeutic category

Table 4.42 indicates the distribution of the different therapeutic categories of the asthma medicine items in the two age groups.

Sympathomimetics

Sympathomimetic usage decreased from 2005 to 2008 in both age groups, but it was always the second most prevalent therapeutic category. There was not a large difference between the prevalence in the 0 – 4 years and the > 4 ≤ 11 years age groups. In the 0 – 4 years age group the usage of sympathomimetics decreased with 5.47% from 2005 (n=15107) to 2008 (n=5323) and in the > 4 ≤ 11 years age group it decreased with 3.73% from 2005 (n=24329) to 2008 (n=14264).

Table 4.42: Prevalence of paediatric asthma medication according to therapeutic category

		0 - 4 years		> 4 ≤ 11 years	
Year	**Therapeutic category**	**Number of medicine items**	**%Prevalence of asthma medication***	**Number of medicine items**	**%Prevalence of asthma medication***
2005	**Sympathomimetics**	15107	**25.75%**	24329	**25.77%**
	Methylxanthines	10125	**17.26%**	21658	**22.94%**
	Anticholinergics	2080	**3.55%**	1304	**1.38%**
	Combinations	18498	**31.54%**	27251	**28.87%**
	Glucocorticoids	6130	**10.45%**	11241	**11.91%**
	Leukotriene receptor antagonists	4803	**8.19%**	6124	**6.49%**
	Other anti-asthmatics	1915	**3.26%**	2496	**2.64%**
2006	**Sympathomimetics**	15936	**25.06%**	26742	**26.22%**
	Methylxanthines	10285	**16.17%**	21743	**21.32%**
	Anticholinergics	2046	**3.22%**	1360	**1.33%**
	Combinations	20045	**31.52%**	29446	**28.87%**
	Glucocorticoids	6438	**10.12%**	11782	**11.55%**
	Leukotriene receptor antagonists	6862	**10.79%**	8584	**8.42%**
	Other anti-asthmatics	1979	**3.11%**	2344	**2.30%**
2007	**Sympathomimetics**	12090	**22.85%**	21171	**25.27%**
	Methylxanthines	6902	**13.04%**	15173	**18.11%**
	Anticholinergics	1821	**3.44%**	1274	**1.52%**
	Combinations	17089	**32.30%**	25100	**29.95%**
	Glucocorticoids	5997	**11.33%**	9792	**11.69%**
	Leukotriene receptor antagonists	7777	**14.70%**	9682	**11.55%**
	Other anti-asthmatics	1235	**2.33%**	1602	**1.91%**
2008	**Sympathomimetics**	5323	**20.28%**	14264	**22.04%**
	Methylxanthines	3364	**12.82%**	11535	**17.82%**
	Anticholinergics	742	**2.83%**	923	**1.43%**
	Combinations	8770	**33.41%**	20546	**31.75%**
	Glucocorticoids	3022	**11.51%**	7343	**11.35%**
	Leukotriene receptor antagonists	4543	**17.31%**	9114	**14.08%**
	Other anti-asthmatics	482	**1.84%**	990	**1.53%**

* %Prevalence of asthma medication is calculated by dividing number of medicine items per therapeutic category per year by the total number of asthma medicine items that was dispensed multiplied by 100.

Methylxanthines

The usage of methylxanthines was always lower in the younger age group (0 – 4 years) than in the older paediatric group (> 4 ≤ 11 years). This may be due to the fact that theophylline has an unpredictable toxicity and children are more prone to the adverse effects of theophylline (Rossiter, 2010:542). These products are also being phased out, therefore the usage have been decreasing from 2005 to 2008 (refer to table 4.42). In the 0 – 4 years age group the prevalence of methylxanthines has decreased from 17.26% in 2005 to 12.82% in 2008. In the > 4 ≤ 11 years age group it decreased by 5.12% from 2005 (n=21658) to 2008 (n=11535).

Anticholinergics

Table 4.42 shows that anticholinergics are not a popular choice for the treatment of paediatric asthma. In children aged > 4 ≤ 11 years the prevalence of anticholinergic usage never even exceeded 1.52% and usage remained fairly constant throughout the study period. In the 0 – 4 years age group it was used the most in 2005 (3.55%) and the least in 2008 (2.83%). Ipratropium, which is the most widely used anticholinergic, is very seldom sold as a single product and is incorporated into combinations with other products.

Combination products

Combination products were the most widely used therapeutic category in both age groups according to table 4.42. This includes a variety of products that consist of long and short-acting β_2-agonists, glucocorticoids and anticholinergics. Some of the cough mixtures are also included in this category, because of their bronchodilator properties. Combination products were used slightly more by the 0 – 4 years age group. Its usage increased with 1.87% in the 0 – 4 years age group from 2005 (n=18498) to 2008 (n=8770) and in the > 4 ≤ 11 years age group it increased with 2.88% from 2005 (n=27251) to 2008 (n=20546).

Glucocorticoids

Glucocorticoids are part of the anti-asthmatic group. It was the most widely used anti-asthmatic until 2007 when leukotriene receptor antagonists surpassed this group. There was an increase in glucocorticoid usage in the 0 – 4 years age group of 1.06% from 2005 (n=6130) to 2008 (n=3022). In the > 4 ≤ 11 years age group it decreased very slightly from 2005 (n=11241) to 2008 (n=7343) with 0.56%.

Leukotriene receptor antagonists

Table 4.42 shows that this is the group that had the biggest advance during the study period. It was used more in the 0 – 4 years age group and had an increase of 9.12% from 2005 (n=4803) to 2008 (n=4543) in this group. The prevalence was not as high in the > 4 ≤ 11 years age group, but still showed an increase from 6.49% in 2005 to 14.08% in 2008. By 2008 it was the anti-asthmatic group that was most widely used in both age groups.

Other anti-asthmatics

This group includes ketotifen, which is used more often for allergies. It was not used often in the study period by both age groups. By the end of 2008 the prevalence decreased to 1.84% and 1.53% in the 0 – 4 years and the > 4 ≤ 11 years age groups respectively.

Table 4.43: Summary of increases and decreases of therapeutic groups from 2005 to 2008 in both age groups

0 – 4 years	
Sympathomimetics	↓
Methylxanthines	↓
Anticholinergics	↓
Combinations	↑
Glucocorticoids	↑
Leukotriene receptor antagonists	↑
Other anti-asthmatics	↓

> 4 ≤ 11 years	
Sympathomimetics	↓
Methylxanthines	↓
Anticholinergics	↑
Combinations	↑
Glucocorticoids	↓
Leukotriene receptor antagonists	↑
Other anti-asthmatics	↓

4.5.6.3 Active ingredient

4.5.6.3.1 Bronchodilators

0 – 4 years of age

Table 4.44 indicates the bronchodilator active ingredients that were issued to children aged 0 – 4 years. The top 5 remained the same throughout the study period. When comparing the results of this age group to the results of the total asthma database (refer to tables 4.11 – 4.14) some differences can be seen. In the paediatric age group fenoterol and ipratropium/salbutamol were included in the top 5 in the study period, which were not in the top 5 of the total asthma database. Salmeterol/fluticasone and theophylline were not as prevalent among the 0 – 4 years age group.

The bromhexine/orciprenaline combination was the active ingredient that was prescribed the most. However, this combination is more often used for cough and is classified under 10.2 in the MIMS® because of its bronchodilator properties (Snyman, 2009a:171). Salbutamol is the first ingredient on the list that is available in oral as well as inhalation form. By 2008 its prevalence decreased by 1.04%, making up 19.19% of all bronchodilator medicine items in this age group. Theophylline/etophylline usage decreased from 2005 (n=8247) to 2008 (n=2843) with 2.38%. It is also used more often for cough and as an expectorant. Fenoterol is a short-acting β_2-agonist, like salbutamol, and was also among the top 5 active ingredients from 2005 to 2008. It was used more often by children in this age group than the total asthma population, as it was ranked higher among the paediatric medicine items. The combination of ipratropium and salbutamol was also used more frequently in the 0 – 4 years age group, than in the total asthma database. It had a prevalence of 12.94% in 2008 in this age group, compared to 4.94% in 2008 in the total asthma database.

Table 4.44: Prevalence of bronchodilators according to active ingredient during in the 0 – 4 years age group

Active ingredient	2005		2006		2007		2008	
	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*
Bromhexine/Orciprenaline	11415	**24.92%**	12217	**25.29%**	10036	**26.48%**	4533	**24.91%**
Salbutamol	9269	**20.23%**	9334	**19.32%**	7406	**19.54%**	3493	**19.19%**
Theophylline/Etophylline	8247	**18.00%**	8442	**17.47%**	5574	**14.71%**	2843	**15.62%**
Fenoterol	4380	**9.56%**	4865	**10.07%**	3850	**10.16%**	1647	**9.05%**
Ipratropium/Salbutamol	4302	**9.39%**	4894	**10.13%**	4628	**12.21%**	2355	**12.94%**
Ipratropium	2080	**4.54%**	2046	**4.23%**	1821	**4.80%**	742	**4.08%**
Theophylline	1871	**4.08%**	1839	**3.81%**	1322	**3.49%**	519	**2.85%**
Salmeterol/Fluticasone	1488	**3.25%**	1815	**3.76%**	1779	**4.69%**	1194	**6.56%**
Fenoterol/Ipratropium	584	**1.27%**	550	**1.14%**	257	**0.68%**	116	**0.64%**
Terbutaline/Guaifenesin	570	**1.24%**	453	**0.94%**	323	**0.85%**	163	**0.90%**
Hexoprenaline	295	**0.64%**	357	**0.74%**	60	**0.16%**	9	**0.05%**
Clobutinol/Orciprenaline	125	**0.27%**	104	**0.22%**	62	**0.16%**	0	**0.00%**
Salmeterol	72	**0.16%**	65	**0.13%**	39	**0.10%**	15	**0.08%**
Other	1112	**2.43%**	1331	**2.76%**	745	**1.97%**	570	**3.13%**

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items of each active ingredient in each year multiplied by 100.

> 4 ≤ 11 years of age

The top 5 active ingredients in the 0 – 4 years and > 4 ≤ 11 years age groups were very similar (refer to table 4.44 & 4.45). Salmeterol/fluticasone played a bigger part in the items for the > 4 ≤ 11 years age group. Theophylline/etophylline was the active ingredient prescribed the most in this age group for 2005 and 2006. Its usage did, however, decrease from 2005 (n=18625) to 2008 (n=9787) by 4.28%, and in 2007 and 2008 it was surpassed by salbutamol. Salbutamol had the highest prevalence in 2007, when it made up 23.06% of bronchodilator medicine items. It was also the highest ranked single active ingredient, because the rest of the top 5 consisted of combination products by 2008.

Fenoterol did not have a prevalence quite as high in this age group as in the 0 – 4 years age group. In the 0 – 4 years age group, fenoterol had a prevalence between 9% and 11% from 2005 to 2008. The older children age group in contrast showed a prevalence between 6% and 7.5% only for fenoterol.

Sameterol/fluticasone, which is a long-acting β_2-agonist and corticosteroid combination, had a presence among the top prescribed active ingredients in this age group. It was not prescribed to the 0 – 4 years age group as often. The prevalence of salmeterol/fluticasone also showed an increase of 3.77% from 2005 (n=5680) to 2008 (n=5383).

The prevalence of salmeterol and formoterol as monotherapies was low. They are the only long-acting β_2-agonists. These products are not allowed to be prescribed as monotherapy anymore, because of the serious asthma exacerbations and asthma-related deaths that occurred due to these products (refer to section 2.5.1.1). Therefore, it is a good sign that salmeterol and formoterol prevalence is already low. Salmeterol had a prevalence of only 0.31% and formoterol a prevalence of 0.36% by the end of 2008.

Table 4.45: Prevalence of bronchodilators according to active ingredient during in the > 4 ≤ 11 years age group

Active ingredient	2005		2006		2007		2008	
	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*
Theophylline/Etophylline	18625	**24.99%**	18758	**23.66%**	12846	**20.48%**	9787	**20.71%**
Salbutamol	15774	**21.16%**	16821	**21.21%**	14463	**23.06%**	10212	**21.60%**
Bromhexine/Orciprenaline	13723	**18.41%**	14595	**18.41%**	12202	**19.46%**	8841	**18.70%**
Salmeterol/Fluticasone	5680	**7.62%**	6547	**8.26%**	6162	**9.82%**	5383	**11.39%**
Fenoterol	4964	**6.66%**	5899	**7.44%**	4596	**7.33%**	3160	**6.69%**
Ipratropium/Salbutamol	4846	**6.50%**	5377	**6.78%**	4777	**7.62%**	3889	**8.23%**
Theophylline	2973	**3.99%**	2936	**3.70%**	2286	**3.64%**	1732	**3.66%**
Ipratropium	1304	**1.75%**	1358	**1.71%**	1274	**2.03%**	923	**1.95%**
Terbutaline/Guaifenesin	1197	**1.61%**	1014	**1.28%**	675	**1.08%**	460	**0.97%**
Fenotrerol/Ipratropium	990	**1.33%**	1050	**1.32%**	657	**1.05%**	463	**0.98%**
Budesonide/Formoterol	560	**0.75%**	634	**0.80%**	481	**0.77%**	463	**0.98%**
Salmeterol	523	**0.70%**	459	**0.58%**	378	**0.60%**	146	**0.31%**
Hexoprenaline	272	**0.36%**	309	**0.39%**	79	**0.13%**	7	**0.01%**
Clobutinol/Orciprenaline	255	**0.34%**	229	**0.29%**	146	**0.23%**	1	**0.00%**
Formoterol	162	**0.22%**	158	**0.20%**	140	**0.22%**	164	**0.35%**
Terbutaline	151	**0.20%**	185	**0.23%**	104	**0.17%**	47	**0.10%**
Other	2543	**3.41%**	2962	**3.74%**	1452	**2.32%**	1590	**3.36%**

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items of each active ingredient in each year multiplied by 100.

4.5.6.3.2 Anti-asthmatics

0 – 4 years of age

When looking at table 4.46, there is a clear front-runner in the anti-asthmatic category among children aged 0 – 4 years. Montelukast, the most well-known leukotriene receptor antagonist, was the active ingredient that was prescribed most frequently. From 2005 (n=4803) to 2008 (n=4543) it showed an increase of 19.08% and comprised 56.46% of all anti-asthmatic medicine items in this age group by the end of 2008. Montelukast is more advantageous to use, as was discussed in a previous chapter (refer to section 2.5.2.3). It was also used less according to the total asthma database as seen in tables 4.16 – 4.19.

Budesonide, the most prescribed corticosteroid, in contrast showed a decrease as it was being used less as the preventer medication of choice. Its prevalence decreased with 6.7% from 2005 (n=4691) to 2008 (n=2399). It was still being used far more than the other glucocorticoids that are used to prevent asthma. By the end of 2008 its prevalence stood at 29.81%. Fluticasone and beclomethasone did not have a high prevalence in this age group and their usages decreased from 2005 to 2008. Beclomethasone was used more often by the total asthma population than in children. In table 4.19 it can be seen that beclomethasone had a prevalence of 13.64% in 2008. Table 4.46 indicates that beclomethasone made up only 0.82% of anti-asthmatic medicine items in children aged 0 – 4 years in 2008. Ciclesonide has only been used since 2006 and does not have a high prevalence.

Ketotifen had a higher prevalence among children aged 0 – 4 years. It is useful in children that suffer from allergic asthma and have trouble using inhalers. Children as young as six months can use ketotifen (refer to section 2.5.3). This may be the reasons for the higher prevalence of ketotifen usage in the young paediatric age group. However, ketotifen usage decreased significantly from 2005 (n=1915) to 2008 (n=482) by 8.92%.

Table 4.46: Prevalence of anti-asthmatics according to active ingredient during in the 0 – 4 years age group

Active ingredient	2005		2006		2007		2008	
	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*
Montelukast	4803	**37.38%**	6862	**44.91%**	7777	**51.82%**	4543	**56.46%**
Budesonide	4691	**36.51%**	5141	**33.65%**	4835	**32.21%**	2399	**29.81%**
Ketotifen	1915	**14.91%**	1979	**12.95%**	1235	**8.23%**	482	**5.99%**
Fluticasone	1123	**8.74%**	1004	**6.57%**	973	**6.48%**	524	**6.51%**
Beclomethasone	316	**2.46%**	287	**1.88%**	169	**1.13%**	66	**0.82%**
Ciclesonide	0	**0.00%**	6	**0.04%**	20	**0.13%**	33	**0.41%**

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items of each active ingredient in each year multiplied by 100.

Table 4.47: Prevalence of bronchodilators according to active ingredient during in the > 4 ≤ 11 years age group

Active ingredient	2005		2006		2007		2008	
	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*	Number of medicine items (N)	% Medicine items*
Budesonide	6938	**34.93%**	7726	**34.02%**	6667	**31.63%**	5037	**28.87%**
Montelukast	6123	**30.83%**	8584	**37.80%**	9681	**45.93%**	9114	**52.24%**
Fluticasone	2836	**14.28%**	2442	**10.75%**	1917	**9.10%**	1480	**8.48%**
Ketotifen	2496	**12.57%**	2344	**10.32%**	1602	**7.60%**	990	**5.67%**
Beclomethasone	1467	**7.39%**	1584	**6.97%**	1121	**5.32%**	729	**4.18%**
Zafirlukast	1	**0.01%**	0	**0.00%**	1	**0.00%**	0	**0.00%**
Ciclesonide	0	**0.00%**	30	**0.13%**	87	**0.41%**	97	**0.56%**

*** %**Medicine items is calculated by dividing the number of medicine items (N) by the sum of the number of medicine items of each active ingredient in each year multiplied by 100.

> 4 ≤ 11 years of age

In table 4.47 the trends of the prescribing patterns of the anti-asthmatics in children aged > 4 ≤ 11 years can be seen. Budesonide followed the same pattern in both age groups, where it was surpassed by montelukast as the most prescribed anti-asthmatic. Budesonide was mostly prescribed in 2005, when it made up 34.93% of the anti-asthmatic medicine items.

Montelukast made up 52.24% of anti-asthmatic medicine items in this age group. Its prevalence also had a sudden increase, as was seen in the 0 – 4 years age group (refer to table 4.46). From 2005 (n=6123) to 2008 (n=9114) there was an increase of 21.41% in the prevalence and the number of medicine items for montelukast also increased, despite the fact that the number of medicine items on the total database decreased.

Fluticasone had a higher prevalence in the 4 ≤ 11 years age group than in the 0 – 4 years age group. In the older age group it made up 8.48% of medicine items in 2008, while in the younger age group only 6.51% of medicine items contained fluticasone. Beclomethasone and fluticasone once again showed a decrease in prevalence. Ciclesonide had a low prevalence and was not used much during the study period.

Ketotifen was also used more often in this age group than in the total asthma population, but the prevalence decreased from 2005 (n=2496) to 2008 (n=990) by 6.90%.

Zafirlukast was used in this age group, where it was not prescribed in the 0 – 4 years age group. There were, however, only 2 zafirlukast prescriptions during the entire study period. The safety of zafirlukast has not been established in children under 12 years of age, which would explain the low prevalence of this drug (Rossiter, 2010:544).

4.5.6.4 Trade names

0 – 4 years of age

Table 4.48 illustrates the top 20 asthma medication trade names used by children aged 0 – 4 years in 2005. These products include medicines from group 10.2 and 10.4. Alcophyllex® (theophylline and etophylline), Adco-Linctopent® (bromhexine and orciprenaline) and Bisolvon® Linctus (bromhexine and orciprenaline) all appear among the top 5, but they are more often used for cough than bronchodilation. Singulair® 4mg tablet (montelukast) was the highest ranked product from group 10.4, followed by Pulmicort® nebulising suspension (budesonide) in position seven. Venteze® syrup (salbutamol) was in the third position and the first bronchodilator on the list. The first inhaler on the list, at position 16, was Seretide® , which is a combination of salmeterol and fluticasone. This shows that very young children are prescribed a syrup or inhalation solution (UDV and nebulising suspensions), rather than an inhalation device.

Table 4.48: The top 20 asthma medication trade names used by children aged 0 – 4 years in 2005

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	7746	13.21%
2	Singulair® 4mg Tab	4279	7.29%
3	Venteze® Syr	4176	7.12%
4	Adco-Linctopent® Syr	4154	7.08%
5	Bisolvon® Linctus	3616	6.16%
6	Berotec® Syr	3208	5.47%
7	Pulmicort® 0.25mg Neb	2734	4.66%
8	Combivent® UDV	2558	4.36%
9	Asthavent® Syr	2503	4.27%
10	Bronkese Co® Syr	1938	3.30%
11	Atrovent® Paed UDV	1653	2.82%
12	Flemeze® Syr	1544	2.63%
13	Duolin® Respules	1448	2.47%
14	Alcophyllin® Syr	1034	1.76%
15	Berotec® Paed UDV	872	1.49%
16	Seretide® 25/125 Inh	770	1.31%
17	Asthavent® 200D Inh	760	1.30%
18	Venteze® 200D Inh	754	1.29%
19	Zetofen® Syr	715	1.22%
20	Nuelin® Liq	635	1.08%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2005 (58658) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

The top 5 of 2006 consisted of only two cough syrups, two short-acting β_2-agonists and a leukotriene receptor antagonist (refer to table 4.49). Alcophyllex® was in the top position once again, but its prevalence decreased by 0.86%, followed by Singulair® 4mg tablets, the prevalence of which increased by 1.74% from 2005 to 2006. Venteze® syrup shifted down a position from 2005 to 2006, but Berotec® syrup shifted up a position to number five. The order of the top 20 products did not change much from 2005 to 2006. Seretide® was still the inhaler that was used the most, but it moved up two positions to number 14 (0.44% increase). Zetofen® syrup, as the only ketotifen containing product in the top 20, moved up from number 19 in 2005 to number 16 in 2006.

Table 4.49: The top 20 asthma medication trade names used by children aged 0 – 4 years in 2006

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	7854	12.35%
2	Singulair® 4mg Tab	5745	9.03%
3	Adco-Linctopent® Syr	4439	6.98%
4	Venteze® Syr	4258	6.70%
5	Berotec® Syr	3725	5.86%
6	Bisolvon® Linctus	3612	5.68%
7	Pulmicort® 0.25mg Neb	3265	5.13%
8	Asthavent® Syr	2604	4.09%
9	Bronkese Co® Syr	2451	3.85%
10	Duolin® Respules	2351	3.70%
11	Combivent® UDV	2072	3.26%
12	Atrovent® Paed UDV	1620	2.55%
13	Flemeze® Syr	1569	2.47%
14	Seretide® 25/125 Inh	1111	1.75%
15	Alcophyllin® Syr	1035	1.63%
16	Zetofen® Syr	932	1.47%
17	Berotec® Paed UDV	790	1.24%
18	Venteze® 200D Inh	737	1.16%
19	Asthavent® 200D Inh	700	1.10%
20	Nuelin® Liq	630	0.99%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2006 (63591) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

Table 4.50 demonstrates the top 20 products used in 2007 in children aged 0 – 4 years. Alcophyllex® was still in the top position, but Singulair® 4mg tablets gained some ground, and was second by only 163 medicine items. Singulair® 4mg sprinkles entered as a new product in 2007 and already made it to number nine on the list. This is a very convenient dosage form for small children and infants. Pulmicort® nebulising suspension moved up two positions on the list from 2006 and ended in fifth position. The first inhaled corticosteroid on the list was seen in 2007; Flixotide® (fluticasone) inhaler was in position 19. Duolin® (ipratropium and salbutamol) usage has slowly been climbing since 2005, where it was in 13th position to 8th position in 2007 (increase of 0.96%).

Table 4.50: The top 20 asthma medication trade names used by children aged 0 – 4 years in 2007

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	4987	9.42%
2	Singulair® 4mg Tab	4824	9.12%
3	Adco-Linctopent® Syr	4192	7.92%
4	Venteze® Syr	3496	6.61%
5	Pulmicort® 0.25mg Neb	3395	6.42%
6	Berotec® Syr	2900	5.48%
7	Bisolvon® Linctus	2751	5.20%
8	Duolin® Respules	2466	4.66%
9	Singulair® 4mg Sprinkles	2422	4.58%
10	Asthavent® Syr	2048	3.87%
11	Bronkese Co® Syr	1894	3.58%
12	Combivent® UDV	1719	3.25%
13	Atrovent® Paed UDV	1384	2.62%
14	Flemeze® Syr	1103	2.08%
15	Seretide® 25/125 Inh	1077	2.03%
16	Zetofen® Syr	726	1.37%
17	Alcophyllin® Syr	677	1.28%
18	Berotec® Paed UDV	609	1.15%
19	Flixotide® 125 CFC Free Inh	590	1.11%
20	Solphyllin® Syr	587	1.11%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2007 (52911) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

The final year of the study period saw a change in the most frequently prescribed trade name (refer to table 4.51). Singulair® 4mg tablets occupied the first position increasing by 2.44% from 2007 to 2008, moving Alcophyllex® to the second position. Adco-Linctopent® remained in third position from 2006 to 2008. Pulmicort® nebulising suspension moved up a position to number 4 in 2008, moving Venteze® syrup down to number five. Duolin® respules usage increased to 6th position, which would make the product the bronchodilator that gained the most ground during the study period (seven positions and an increase of 2.56% from 2005 to 2008). Singulair® 4mg sprinkles remained in position number 9 in 2008. Seretide® had two different strengths of products on the list. Seretide® 25/125 inhaler was in 13th position and Seretide® 25/50 inhaler appeared on the list for the first time at number 19. Duro-Tuss® linctus (salbutamol and bromhexine) was also among the top 20 for the first time in 2008 in 16th position.

Table 4.51: The top 20 asthma medication trade names used by children aged 0 – 4 years in 2008

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Singulair® 4mg Tab	3035	11.56%
2	Alcophyllex® Syr	2453	9.35%
3	Adco-Linctopent® Syr	1970	7.51%
4	Pulmicort® 0.25mg Neb	1620	6.17%
5	Venteze® Syr	1535	5.85%
6	Duolin® Respules	1321	5.03%
7	Berotec® Syr	1234	4.70%
8	Bisolvon® Linctus	1207	4.60%
9	Singulair® 4mg Sprinkles	1187	4.52%
10	Asthavent® Syr	926	3.53%
11	Bronkese Co® Syr	850	3.24%
12	Combivent® UDV	827	3.15%
13	Seretide® 25/125 Inh	785	2.99%
14	Atrovent® Paed UDV	583	2.22%
15	Flemeze® Syr	472	1.80%
16	Duro-Tuss® Linctus	404	1.54%
17	Solphyllin® Syr	390	1.49%
18	Asthavent® 200D Inh	356	1.36%
19	Seretide® 25/50 Inh	322	1.23%
20	Alcophyllin® Syr	309	1.18%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2008 (26246) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

> 4 ≤ 11 years of age

The prescribing patterns of the top 20 products in this age group were very similar to those of the 0 – 4 years age group in 2005 (refer to table 4.48 & 4.52). The top 5 included three cough syrups. Alcophyllex® was the most often prescribed (18.26% of medicine items), followed by Adco-Lintopent® in second position and Bisolvon® linctus in fifth position. Venteze® syrup was also used frequently and is the first β_2-agonist on the list in position number three. There is, however, a difference between the age groups when it comes to montelukast. Singulair® 5mg tablets (3.71%) was prescribed in this age group, because this dosage is allowed to be given to children between 6 and 12 years, whilst the 4mg forms of Singulair® (2.47%) was prescribed to children between the ages of 2 and 5 years (Snyman, 2009a:175). Singulair® 5mg was in the fourth position in 2005 and the 4mg variant was in position 11. Inhalers were used more often by this age group. This may be because older children have less trouble understanding and using an inhaler. Asthavent® inhaler was in 10th position. Seretide® had two strengths that were prescribed often. The Seretide® 50/100 accuhaler was in 13th position and the 25/125 inhaler was number 18. A product that was not on the 0 – 4 years list was the Inflammide® (budesonide) inhaler (position 17).

Table 4.52: The top 20 asthma medication trade names used by children aged > 4 ≤ 11 years in 2005

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	17236	18.26%
2	Adco-Linctopent® Syr	5268	5.58%
3	Venteze® Syr	4865	5.15%
4	Singulair® 5mg Tab	3501	3.71%
5	Bisolvon® Linctus	3493	3.70%
6	Berotec® Syr	3466	3.67%
7	Asthavent® Syr	3250	3.44%
8	Combivent® UDV	2741	2.90%
9	Bronkese Co® Syr	2652	2.81%
10	Asthavent 200D Inh	2431	2.58%
11	Singulair® 4mg Tab	2333	2.47%
12	Venteze® 200D Inh	2312	2.45%
13	Seretide® 50/100 Accuhaler	2103	2.23%
14	Flemeze® Syr	1965	2.08%
15	Alcophyllin® Syr	1823	1.93%
16	Pulmicort® 0.25mg Neb	1721	1.82%
17	Inflammide ® 100mcg Inh	1675	1.77%
18	Seretide® 25/125 Inh	1611	1.71%
19	Duolin® Respules	1473	1.56%
20	Solphyllin® Syr	1389	1.47%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2005 (94403) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

In 2006 the products were not greatly altered from 2005 (refer to table 4.53). The first four products remained the same, only Bisolvon® linctus was moved down the list to make way for Berotec® syrup. This means that there were two short-acting β_2-agonists among the top 5. Singulair® 4mg moved up five positions to number six (increase of 1.23% from 2005 to 2006). The Seretide® 50/100 accuhaler was being used less often than in 2005, but did not show a significant decrease in prevalence, while the 25/125 inhaler moved up on the list to number 16 (0.5% increase from 2005 to 2006). The Inflammide® inhaler usage also decreased from 2005 and this product was in 20th position in 2006. Pulmicort® (budesonide) nebulising suspension was used less in the > 4 ≤ 11 years age group than in the 0 – 4 years age group. It was in 15th position in this age group according to table 4.53, but was number seven on the 0 – 4 years' list in the same year.

Table 4.53: The top 20 asthma medication trade names used by children aged > 4 ≤ 11 years in 2006

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	16972	17.98%
2	Adco-Linctopent® Syr	5296	5.61%
3	Venteze® Syr	5247	5.56%
4	Singulair® 5mg Tab	4564	4.83%
5	Berotec® Syr	4285	4.54%
6	Singulair® 4mg Tab	3490	3.70%
7	Bisolvon® Linctus	3470	3.68%
8	Asthavent® Syr	3444	3.65%
9	Bronkese Co® Syr	3291	3.49%
10	Asthavent® 200D Inh	2948	3.12%
11	Duolin® Respules	2311	2.45%
12	Combivent® UDV	2305	2.44%
13	Flemeze® Syr	2244	2.38%
14	Venteze® 200D Inh	2198	2.33%
15	Pulmicort® 0.25mg Neb	2164	2.29%
16	Seretide® 25/125 Inh	2085	2.21%
17	Seretide® 50/100 Accuhaler	2075	2.20%
18	Alcophyllin® Syr	1807	1.91%
19	Solphyllin® Syr	1786	1.89%
20	Inflammide ® 100mcg Inh	1558	1.65%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2006 (102001) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

Table 4.54 shows the top 20 products for 2007 in the > 4 ≤ 11 years age group. Alcophyllex® and Adco-Linctopent® were in the first two positions. Singulair® 5mg moved up a position to number three (increase of 1.13% from 2006 to 2007) and Singulair® 4mg managed to get into the top 5. The Seretide® 25/125 inhaler moved up five positions from 2006 and was 11th in 2007 (increase of 0.69%). Pulmicort® nebulising suspenision also showed an improvement from 2006 and moved up two positions to number 13. An interesting trend among this age group is that inhalers were more often used than inhalation solutions (UDVs). Older children are, therefore more comfortable with inhalers than younger children and inhalers proved to be used more often than accuhalers and other inhalation devices.

Table 4.54: The top 20 asthma medication trade names used by children aged > 4 ≤ 11 years in 2007

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	11125	13.28%
2	Adco-Linctopent® Syr	5082	6.06%
3	Singulair® 5mg Tab	4991	5.96%
4	Venteze® Syr	4733	5.65%
5	Singulair® 4mg Tab	3874	4.62%
6	Berotec® Syr	3297	3.93%
7	Asthavent® Syr	2889	3.44%
8	Bisolvon® Linctus	2690	3.21%
9	Bronkese Co® Syr	2640	3.15%
10	Asthavent® 200D Inh	2542	3.03%
11	Seretide® 25/125 Inh	2429	2.90%
12	Duolin® Respules	2390	2.85%
13	Pulmicort® 0.25mg Neb	2198	2.62%
14	Venteze® 200D Inh	1906	2.27%
15	Combivent® UDV	1725	2.06%
16	Solphyllin® Syr	1721	2.05%
17	Seretide® 50/100 Accuhaler	1667	1.99%
18	Flemeze® Syr	1567	1.87%
19	Alcophyllin® Syr	1338	1.60%
20	Inflammide ® 100mcg Inh	1222	1.46%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2007 (83794) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

In the final year of the study period some changes were seen in the prescribing patterns of the products (refer to table 4.55). Singulair® 5mg was prescribed the second most to patients in this age group (increase of 1.25% from 2007 to 2008) and Singulair® 4mg, despite not being specifically prescribed in older children, was in 4th position (increase of 1.06% from 2007 to 2008). Adco-Linctopent® (number 3) is the generic equivalent of Bisolvon® linctus (number 10) and it can be said that the generic has been prescribed much more often than the original product. Pulmicort® nebulising suspension also moved up from 2007 and moved up four positions from 2005 to 2008 (increase of 1.04%). Duolin® respules, as seen in the 0 – 4 years age group as well, moved up from position 19 in 2005 to 8 in 2008 (increase of 1.57%). This is an indication that rescue or reliever medications are being used more often. Seretide® 25/125 showed an increase from 2005, where it was in position 18, to 2008 where it was 7th (increase of 1.19%). Duro-Tuss® linctus was first used in 2008 and made the list at number 18.

Table 4.55: The top 20 asthma medication trade names used by children aged > 4 ≤ 11 years in 2008

Position	Active ingredient	Number of medicine items (N)	% Medicine items*
1	Alcophyllex® Syr	8083	12.49%
2	Singulair® 5mg Tab	4668	7.21%
3	Adco-Linctopent® Syr	3858	5.96%
4	Singulair® 4mg Tab	3673	5.68%
5	Venteze® Syr	3238	5.00%
6	Berotec® Syr	2333	3.61%
7	Seretide® 25/125 Inh	2154	3.33%
8	Duolin® Respules	2028	3.13%
9	Asthavent® Syr	1980	3.06%
10	Bisolvon® Linctus	1931	2.98%
11	Bronkese Co® Syr	1921	2.97%
12	Pulmicort® 0.25mg Neb	1850	2.86%
13	Asthavent® 200D Inh	1782	2.75%
14	Solphyllin® Syr	1704	2.63%
15	Combivent® UDV	1407	2.17%
16	Venteze® 200D Inh	1246	1.93%
17	Seretide® 50/100 Accuhaler	1236	1.91%
18	Duro-Tuss® Linctus	1046	1.62%
19	Alcophylllin® Syr	1002	1.55%
20	Flemeze® Syr	979	1.51%

* %Medicine items is calculated by dividing N for each trade name by the total asthma medicine items in this age group in 2008 (64715) and multiplying by 100. The percentages will not add up to 100%, because only the top 20 trade names were used.

4.6 Combinations of medication used by asthma patients

4.6.1 Combinations of asthma medication

Asthma patients often do not use only one product to treat their asthma (refer to section 2.4). It is beneficial to use combinations of different products and the medications also have different purposes when it comes to controlling the asthma of the patient.

4.6.1.1 Two products

0 – 4 years of age

Table 4.56 displays the combination of two asthma medications for each year of the study period in the 0 – 4 years age group. Only the top 10 combinations are displayed here. In this age group, different inhalation and nebulising solutions (including UDVs) were often prescribed together. These types of combinations were the most frequently prescribed annually from 2005 to 2008. The Seretide®25/125 inhaler and Singulair® 4mg tablets combination also appeared every year.

> 4 ≤ 11 years of age

Table 4.57 shows the combinations that were prescribed to children aged >4 ≤ 11 years. Once again only the top 10 combinations are displayed. The use of inhalers was prevalent among this age group. Most of the combinations included inhalation products, such as inhaler, accuhalers and nebulising solutions. The only cough syrup included in the top combinations was Alcophyllex® syrup. Venteze®, Asthavent® and Berotec® syrup were the oral bronchodilators that featured. Singulair® 5mg tablets were prescribed in combination with Seretide® inhalers of different strengths. The same combination was also often seen in the 0 – 4 years age group (table 4.56).

Table 4.56: The top combinations of two products prescribed to children aged 0 – 4 years

Year	Product 1	Product 2	Number of prescriptions (N)	% Prescriptions*
2005	Combivent® UDV	Pulmicort® 0.25mg neb	560	1.14%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	312	0.64%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed .5mg	294	0.60%
	Alcophyllex® syr	Venteze® syr	283	0.58%
	Duolin® respules	Pulmicort® 0.25mg neb	274	0.56%
	Alcophyllex® syr	Asthavent® syr	238	0.49%
	Alcophyllex® syr	Berotec® syr	110	0.22%
	Asthavent® inh 200D	Inflammide® 100mcg inh 200D	107	0.22%
	Seretide® 25/125 Inh	Singulair® 4mg tab	95	0.19%
	Combivent® UDV	Pulmicort® 0.5mg neb	86	0.18%
2006	Combivent® UDV	Pulmicort® 0.25mg neb	524	1.00%
	Duolin® respules	Pulmicort® 0.25mg neb	501	0.96%
	Alcophyllex® syr	Venteze® syr	329	0.63%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed .5mg	297	0.57%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	295	0.56%
	Alcophyllex® syr	Asthavent® syr	237	0.45%
	Seretide® 25/125 Inh	Singulair® 4mg tab	206	0.39%
	Alcophyllex® syr	Berotec® syr	157	0.30%
	Seretide® 25/50 Inh	Singulair® 4mg tab	120	0.23%
	Duolin® respules	Singulair® 4mg tab	114	0.21%
2007	Duolin® respules	Pulmicort® 0.25mg neb	615	1.44%
	Combivent® UDV	Pulmicort® 0.25mg neb	492	1.15%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	311	0.73%
	Alcophyllex® syr	Venteze® syr	285	0.67%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed .5mg	193	0.45%
	Seretide® 25/125 Inh	Singulair® 4mg tab	184	0.43%
	Alcophyllex® syr	Asthavent® syr	156	0.36%
	Seretide® 25/50 Inh	Singulair® 4mg tab	118	0.28%
	Berotec® syr	Singulair® sprinkles 4mg	90	0.21%
	Duolin® respules	Singulair® 4mg tab	78	0.18%
2008	Duolin® respules	Pulmicort® 0.25mg neb	314	1.49%
	Combivent® UDV	Pulmicort® 0.25mg neb	256	1.21%
	Alcophyllex® syr	Venteze® syr	153	0.72%
	Seretide® 25/125 Inh	Singulair® 4mg tab	140	0.66%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	113	0.53%
	Seretide® 25/50 Inh	Singulair® 4mg tab	83	0.39%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed .5mg	77	0.36%
	Alcophyllex® syr	Asthavent® syr	73	0.35%
	Seretide® 25/125 Inh	Singulair® sprinkles 4mg	57	0.27%
	Duolin® respules	Singulair® 4mg tab	53	0.25%

*% Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in this age group multiplied by 100.

Table 4.57: The top combinations of two products prescribed to children aged >4 ≤ 11 years

Year	Product 1	Product 2	Number of prescriptions (N)	% Prescriptions*
2005	Alcophyllex® syr	Asthavent® syr	486	0.63%
	Alcophyllex® syr	Venteze ® syr	459	0.59%
	Combivent® UDV	Pulmicort® 0.25mg neb	394	0.51%
	Asthavent® inh 200D	Inflammide® 100mcg inh 200D	284	0.37%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	214	0.28%
	Duolin® respules	Pulmicort® 0.25mg neb	205	0.27%
	Seretide® 50/100 accuhaler	Singulair® 5mg	193	0.25%
	Combivent® UDV	Pulmicort® 0.5mg neb	172	0.22%
	Inflammide® 100mcg inh 200D	Venteze® inh comp 200D	168	0.22%
	Seretide® 25/125 Inh	Singulair® 5mg	156	0.20%
2006	Alcophyllex® syr	Venteze ® syr	584	0.71%
	Alcophyllex® syr	Asthavent® syr	419	0.51%
	Combivent® UDV	Pulmicort® 0.25mg neb	408	0.50%
	Duolin® respules	Pulmicort® 0.25mg neb	367	0.45%
	Asthavent® inh 200D	Inflammide® 100mcg inh 200D	247	0.30%
	Asthavent® inh 200D	Budeflam® HFA 100mcg 300D	235	0.29%
	Alcophyllex® syr	Berotec® syr	195	0.24%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	188	0.23%
	Seretide® 50/100 accuhaler	Singulair® 5mg	181	0.22%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	167	0.20%
2007	Alcophyllex® syr	Venteze ® syr	495	0.74%
	Duolin® respules	Pulmicort® 0.25mg neb	437	0.66%
	Combivent® UDV	Pulmicort® 0.25mg neb	359	0.54%
	Alcophyllex® syr	Asthavent® syr	324	0.49%
	Seretide® 25/125 Inh	Singulair® 4mg tab	277	0.42%
	Seretide® 25/125 Inh	Singulair® 5mg	238	0.36%
	Asthavent® inh 200D	Inflammide® 100mcg inh 300D	224	0.34%
	Asthavent® inh 200D	Budeflam® HFA 100mcg 300D	205	0.31%
	Seretide® 50/250 accuhaler	Singulair® 5mg	204	0.31%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	183	0.28%
2008	Duolin® respules	Pulmicort® 0.25mg neb	381	0.74%
	Alcophyllex® syr	Venteze ® syr	336	0.65%
	Combivent® UDV	Pulmicort® 0.25mg neb	327	0.63%
	Seretide® 25/125 Inh	Singulair® 4mg tab	261	0.50%
	Alcophyllex® syr	Asthavent® syr	239	0.46%
	Seretide® 25/125 Inh	Singulair® 5mg	238	0.46%
	Seretide® 50/250 accuhaler	Singulair® 5mg	166	0.32%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	130	0.25%
	Asthavent® inh 200D	Inflammide® 100mcg inh 300D	124	0.24%
	Seretide® 50/100 accuhaler	Singulair® 5mg	122	0.24%

* %Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in each year in this age group multiplied by 100.

Table 4.58: The top combinations of three products prescribed to children aged 0 – 4 years

Year	Product 1	Product 2	Product 3	Number of prescriptions (N)	% Prescriptions*
2005	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg tab	55	0.11%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	46	0.09%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	Singulair® 4mg tab	25	0.05%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg tab	25	0.05%
	Berotec® syr	Combivent® UDV	Pulmicort® 0.25mg neb	18	0.04%
	Bisolvon® linctus	Combivent® UDV	Pulmicort® 0.25mg neb	18	0.04%
2006	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	69	0.13%
	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg tab	61	0.11%
	Atrovent® UDV paed 0.25mg	Pulmicort® 0.25mg neb	Singulair® 4mg tab	42	0.08%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg tab	37	0.07%
	Alcophyllex® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	29	0.06%
	Inflammide® 100mcg inh 200D	Singulair® 4mg tab	Venteze® inh comp 200D	22	0.04%
2007	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	52	0.12%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg sprinkles	44	0.10%
	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg tab	41	0.10%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg tab	41	0.10%
	Seretide® 25/125 Inh	Singulair® 4mg tab	Venteze® inh comp 200D	33	0.08%
	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg sprinkles	27	0.06%
2008	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg tab	34	0.16%
	Combivent® Inh	Seretide® 25/125 Inh	Singulair® 4mg tab	28	0.13%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	25	0.12%
	Combivent® Inh	Seretide® 25/125 Inh	Singulair® 4mg tab	23	0.11%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg tab	21	0.10%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 4mg sprinkles	15	0.07%

* %Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in each year in this age group.

Table 4.59: The top combinations of three products prescribed to children aged >4 ≤ 11 years

Year	Product 1	Product 2	Product 3	Number of prescriptions (N)	% Prescriptions*
2005	Flixotide® 125 CFC free Inh	Singulair® 5mg	Venteze® inh comp 200D	21	0.03%
	Seretide® 50/250 accuhaler	Singulair® 5mg	Ventolin® accuhaler 200mcg	21	0.03%
	Asthavent® Inh 200D	Flixotide® 125 CFC free Inh	Serevent® inhaler 120	20	0.03%
	Atrovent® 40 compl 300D	Flixotide® accuhaler 100mcg	Serevent® accuhaler	20	0.03%
	Bisolvon® linctus	Combivent® UDV	Pulmicort® 0.25mg neb	17	0.02%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	16	0.02%
2006	Asthavent® Inh 200D	Flixotide® 125 CFC free Inh	Serevent® inhaler 120	22	0.03%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	21	0.03%
	Alcophyllex® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	20	0.02%
	Combivent® Inh	Inflammide® 100mcg inh 200D	Singulair® 5mg	20	0.02%
	Flixotide® 125 CFC free Inh	Serevent® inhaler 120	Singulair® 10mg	20	0.02%
	Combivent® Inh	Inflammide® 100mcg inh 200D	Venteze® inh comp 200D	19	0.02%
2007	Seretide® 50/100 accuhaler	Singulair® 5mg	Ventolin® accuhaler 200mcg	32	0.05%
	Asthavent® Inh 200D	Seretide® 25/125 Inh	Singulair® 5mg	29	0.04%
	Seretide® 25/125 Inh	Singulair® 4mg tab	Ventolin® inh 200D CFC-free	27	0.04%
	Asthaven®t Inh 200D	Budeflam® HFA 100mcg 300D	Singulair® 4mg tab	25	0.04%
	Flixotide® 125 CFC free Inh	Singulair® 4mg tab	Venteze® inh comp 200D	23	0.03%
	Seretide® 50/250 accuhaler	Singulair® 5mg	Ventolin® accuhaler 200mcg	23	0.03%
2008	Seretide® 50/100 accuhaler	Singulair® 5mg	Ventolin® accuhaler 200mcg	39	0.08%
	Seretide® 25/125 Inh	Singulair® 4mg tab	Venteze® inh comp 200D	34	0.07%
	Asthaven®t Inh 200D	Seretide® 25/125 Inh	Singulair® 4mg tab	26	0.05%
	Duolin® respules	Pulmicort® 0.25mg neb	Singulair® 5mg	25	0.05%
	Seretide® 50/250 accuhaler	Singulair® 5mg	Ventolin® accuhaler 200mcg	25	0.05%
	Asthavent® Inh 200D	Seretide® 25/125 Inh	Singulair® 5mg	23	0.04%

* %Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in each year in this age group.

4.6.1.2 Three products

0 – 4 years of age

Pulmicort® nebulising suspension and Singulair® 4mg tablets were the two products that appeared the most frequently in the combination of three products in children aged 0 – 4 years of age (refer to table 4.58). The paediatric dose of both these products were given, 0.25mg/ml for Pulmicort® and 4mg Singulair® tablets. Most of these combinations contained the following types of medication: a bronchodilator (Atrovent®, Duolin® or Combivent®), a corticosteroid (Pulmicort®) and a leukotriene receptor antagonist (Singulair®).

> 4 ≤ 11 years of age

The combination of three products in children aged > 4 ≤ 11 years can be seen in table 4.59. A wider variety of combinations can be seen in this age group, compared to the limited number of products in the 0 – 4 years age group (refer to table 4.58). Accuhalers and inhalers played a definite role in these combinations. The combination of a bronchodilator, an anti-asthmatic and a combination product was seen in many of the most prescribed cases in table 4.59.

4.6.1.3 Four products

0 – 4 years of age

In table 4.60 the combination of four products prescribed to children aged 0 – 4 years can be seen. Prescriptions with more than one asthma medicine item on are becoming less frequent the more products are added to the prescription. Singulair® 4mg tablets were almost always included in these prescriptions, which corresponds with the prescribing patterns and high prevalence of this product. Inhalers and nebulising solutions were prescribed together in most cases. In all the different combinations, there was at least one controller medication (e.g. Singulair®, Pulmicort®). The frequency of relievers (Berotec®, Atrovent®) and combination products (Seretide®) varied.

> 4 ≤ 11 years of age

Table 4.61 indicates the combination of four asthma products in the > 4 ≤ 11 years age group. In cases where children have to receive many types of medication, the child has severe asthma. In 2005 Foradil® inhalers were prescribed in combination with other products. This relates to the research on the safety of long-acting β_2-agonists and that they should not be prescribed as monotherapy (Nelson *et al*., 2006:26; Mann *et al*., 2003:70). The same types of medication combinations were seen in both paediatric age groups. Bronchodilators and anti-asthmatics were prescribed together. The cases in which there was not an anti-asthmatic prescribed, a combination product (Seretide® or Symbicord®) made up a part of the prescription.

Table 4.60: The top combinations of four products prescribed to children aged 0 – 4 years

Year	Product 1	Product 2	Product 3	Product 4	Number of prescriptions (N)	% Prescriptions*
2005	Becotide® 100 inh comp	Berotec® inh comp 300D	Flixotide® 125 CFC free Inh	Singulair® 4mg tab	5	0.010%
	Berotec® syr	Combivent® UDV	Pulmicort® 0.25mg neb	Singulair® 4mg tab	3	0.006%
	Duolin® respules	Flemeze® syr	Seretide® 25/125 Inh	Singulair® 4mg tab	3	0.006%
2006	Pulmicort® 0.25mg neb	Seretide® 25/125 Inh	Singulair® 4mg tab	Ventolin® 2.5mg neb	7	0.013%
	Berodual® 200D inh	Inflammide® 100mcg inh 200D	Seretide® 25/125 Inh	Singulair® 4mg tab	6	0.011%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Bisolvon® linctus	Pulmicort® 0.25mg neb	5	0.010%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	Singulair® 4mg tab	5	0.010%
2007	Berodual® 200D inh	Inflammide® 100mcg inh 300D	Seretide® 25/125 Inh	Singulair® 4mg tab	11	0.026%
	Pulmicort® 0.25mg neb	Seretide® 25/125 Inh	Singulair® 4mg tab	Ventolin® 2.5mg neb	10	0.023%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Bisolvon® linctus	Pulmicort® 0.25mg neb	5	0.012%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	Singulair® 4mg tab	5	0.012%
2008	Adco-Ketotifen® syr	Berotec® UDV paed 0.5mg	Flixotide® 125 CFC free Inh	Singulair® 4mg tab	8	0.038%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Pulmicort® 0.25mg neb	Singulair® 4mg tab	3	0.014%
	Pulmicort® 0.25mg neb	Seretide® 25/125 Inh	Singulair® 4mg tab	Ventolin® 2.5mg neb	3	0.014%

* %Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in each year in this age group.

Table 4.61: The top combinations of four products prescribed to children aged >4 ≤ 11 years

Year	Product 1	Product 2	Product 3	Product 4	Number of prescriptions	% Prescriptions*
2005	Bricanyl® inh comp	Budeflam® HFA 100mcg 300D	Foradil® inhaler 100D	Singulair® 5mg	6	0.008%
	Alcophyllex® syr	Asthavent® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	4	0.005%
	Berodual® 200D inh	Combivent® UDV	Inflammide® 200mcg inh	Singulair® 5mg	4	0.005%
2006	Alcophyllex® syr	Asthavent® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV adult 1.25mg	5	0.006%
	Alcophyllex® syr	Asthavent® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	4	0.005%
	Asthavent® Inh 200D	Atrovent® beta UDV	Beclate® 100mcg inh 200D	Berotec® UDV paed 0.5mg	4	0.005%
	Duovent® inh 300D	Flixotide® 125 CFC free Inh	Sabax Fenoterol® 0.5mg/2ml	Sabax Ipratropium® 0.25mg/2ml	4	0.005%
2007	Beclate® 200mcg inh 200D	Sandoz Theophylline® 200mg	Serevent® inhaler 120	Venteze® inh comp 200D	9	0.014%
	Berotec® inh comp 300D	Flixotide® 125 CFC free Inh	Pulmicort® 0.25mg neb	Singulair® 4mg tab	9	0.014%
	Alcophyllex® syr	Asthavent® syr	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	6	0.009%
	Atrovent® UDV paed 0.25mg	Berotec® UDV paed 0.5mg	Nuelin® liquid	Symbicord® turbuhaler 160/4.5 60D	5	0.008%
2008	Duovent® HFA inh 200D	Inflammide® 100mcg inh 300D	Serevent® inhaler 60	Singulair® 5mg	12	0.023%
	Berodual® 200D inh	Inflammide® 100mcg inh 300D	Seretide® 25/125 Inh	Singulair® 4mg tab	11	0.021%
	Berotec® inh comp 300D	Flixotide® 125 CFC free Inh	Pulmicort® 0.25mg neb	Singulair® 4mg tab	7	0.014%
	Duovent® HFA inh 200D	Nuelin® liquid	Seretide® 25/125 Inh	Singulair® 5mg	7	0.014%

* %Prescriptions is calculated by dividing N by the total asthma prescriptions for each combination in each year in this age group.

4.6.2 Combinations of asthma medication, antibiotics and corticosteroids

Children with asthma often receive other medications because of their asthma (refer to section 2.5.5). These medications are not necessarily beneficial in the treatment of asthma, but they are mostly prescribed during asthma exacerbations (Laforest *et al.*, 2008:58).

4.6.2.1 Frequently prescribed antibiotics

Antibiotics are often dispensed to children with asthma. Upper respiratory tract infections could occur because of uncontrolled asthma, which must then be treated with antibiotics (Laforest *et al.*, 2008:58). Therefore, the antibiotics that are mainly used against respiratory tract infections are dispensed the most frequently to children according to tables 4.62 and 4.63.

Table 4.62: The most frequently prescribed antibiotics in children aged 0 – 4 years with asthma from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Amoxicillin/Clavulanic acid	22835	13.82%
Amoxicillin	15847	9.59%
Cefpodoxime	15274	9.24%
Clarithromycin	6281	3.80%
Cefuroxime	4475	2.71%
Azithromycin	4427	2.68%
Cefprozil	4128	2.50%
Erythromycin	3757	2.27%
Trimethoprim/Sulphametoxazole	2883	1.74%
Cefaclor	2048	1.24%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.63: The most frequently prescribed antibiotics in children aged >4 ≤ 11 years with asthma from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Amoxicillin/Clavulanic acid	44660	16.09%
Amoxicillin	27239	9.82%
Cefpodoxime	15684	5.65%
Clarithromycin	9730	3.51%
Erythtomycin	6766	2.44%
Cefuroxime	6611	2.38%
Azithromycin	4753	1.71%
Cefprozil	4233	1.53%
Trimethoprim/Sulphametoxazole	3702	1.33%
Cefaclor	2939	1.06%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

Amoxicillin in combination with clavulanic acid (also known as co-amoxiclav) was the antibiotic that was used the most in both age groups, but slightly more in the >4 ≤ 11 years age group. Amoxicillin without clavulanic acid was dispensed the second most. This antibiotic is mainly used for respiratory tract infections (Rossiter, 2010:280). Cefpodoxime is a third-generation cephalosporin and can be used against pneumonia and other organisms that cause respiratory infections. Cefuroxime, cefprozil and cefachlor are second generation cephalosporins and are used against many Gram-positive and –negative organisms (Rossiter, 2010:285). The three macrolides that were also dispensed frequently to children were clarithromycin, erythromycin and azithromycin and are used against the more resistant types of respiratory tract infections. Trimethoprim/sulphametoxazole is the only sulphonamide combination that is frequently used. It can act against upper respiratory infections, but is used more widely for skin infections and urinary tract infections. It is, however, a very inexpensive antibiotic (Snyman, 2009b:263).

4.6.2.2 Frequently prescribed corticosteroids

In case of a severe asthma attack or exacerbation children will receive systemic corticosteroids. This brings the asthma attack under control again. Children with severe asthma who contract a viral respiratory infection will also be prescribed oral corticosteroids (refer to section 2.4). This treatment of asthma is recommended to be used only in emergencies and not as a regular method to control asthma, because of the side-effects systemic corticosteroids may cause especially in children (refer to section 2.5.2.1). Tables 4.64 and 4.65 display the systemic corticosteroids that were frequently prescribed to paediatric asthma patients from 2005 to 2008.

Table 4.64: The most frequently prescribed systemic corticosteroids in children aged 0 – 4 years with asthma from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Prednisolone	18050	10.92%
Betamethasone	6886	4.17%
Betamethasone/Dexchlorpheniramine	6597	3.99%
Prednisone	1287	0.78%
Hydrocortisone	69	0.04%
Dexamethasone	21	0.01%
Methylprednisolone	6	0.00%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.65: The most frequently prescribed systemic corticosteroids in children aged >4 ≤ 11 years with asthma from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Prednisolone	19721	7.11%
Betamethasone	9676	3.49%
Prednisone	8554	3.08%
Betamethasone/Dexchlorpheniramine	7417	2.67%
Methylprednisolone	147	0.05%
Hydrocortisone	122	0.04%
Dexamethasone	40	0.01%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

Prednisolone is available as a syrup. This may be the reason for its high frequency, especially in the 0 – 4 years age group, because it is a convenient dosage form. Betamethasone and betamethasone/dexchlorpheniramine syrups are also suitable to use in children that are not able to swallow a tablet. Betamethasone/dexchlorpheniramine (Celestamine®) can be used to treat allergic reactions as well (Snyman, 2009c:306). Methylprednisolone and prednisone are only available to inject or in tablet form. That is why it was prescribed more often in the older paediatric age group than the younger group (tables 4.64 & 4.65). The disadvantage of dexamethasone is that it is only available as an injection, which means that the patients do not administer the medication themselves and are often hospitalised when receiving this medication. It is, therefore, not dispensed often.

4.6.2.3 Asthma products in combination with other medication

One product

Tables 4.66 and 4.67 illustrate the number of prescriptions where the asthma products were prescribed alone according to active ingredient.

Table 4.66: The most frequently prescribed asthma medications prescribed alone in children aged 0 – 4 years from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Bromhexine/Orciprenaline	14117	8.54%
Montelukast	10937	6.62%
Salbutamol	5425	3.28%
Theophylline/Etophylline	5222	3.16%
Fluticasone	3457	2.09%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.67: The most frequently prescribed asthma medications prescribed alone in children aged >4 ≤ 11 years from 2005 to 2008

Active ingredient	Number of prescriptions (N)	% Prescriptions*
Bromhexine/Orciprenaline	16619	5.99%
Montelukast	15468	5.57%
Fluticasone	14227	5.13%
Theophylline/Etophylline	13848	4.99%
Salbutamol	9740	3.51%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

The cough syrups and bronchodilators, bromhexine/orciprenaline and theophylline and etophylline were dispensed often (tables 4.66 & 4.67). Montelukast was still prescribed in both age groups, but it had a higher prevalence in the 0 – 4 years age group. Fluticasone, the corticosteroid, was more frequently prescribed to older children, while salbutamol had a higher prevalence in the younger paediatric group.

Two products

When looking at the most frequently prescribed combinations of asthma medication with other medications, there are some points to consider (refer to tables 4.68 & 4.69).

Every combination included an active ingredient that is essentially used as a cough medicine, theophylline/etophylline and bromhexine/orciprenaline. These products contain bronchodilators and for this reason they are included in group 10.2.

Table 4.68: The top 10 combinations of two products prescribed together to children aged 0 – 4 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Number of prescriptions (N)	% Prescriptions*
Theophylline/Etophylline	Amoxicillin	5096	3.08%
Theophylline/Etophylline	Amoxicillin/Clavulanic acid	4294	2.60%
Bromhexine/Orciprenaline	Amoxicillin/Clavulanic acid	4102	2.48%
Bromhexine/Orciprenaline	Cefpodoxime	3331	2.02%
Amoxicillin/Clavulanic acid	Salbutamol	2602	1.57%
Bromhexine/Orciprenaline	Amoxicillin	2369	1.43%
Amoxicillin	Salbutamol	2253	1.36%
Theophylline/Etophylline	Erythromycin	926	0.56%
Bromhexine/Orciprenaline	Clarithromycin	906	0.55%
Bromhexine/Orciprenaline	Cefuroxime	1305	0.79%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.69: The top 10 combinations of two products prescribed together to children aged >4 ≤ 11 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Number of prescriptions (N)	% Prescriptions*
Theophylline/Etophylline	Amoxicillin	11469	4.13%
Theophylline/Etophylline	Amoxicillin/Clavulanic acid	10870	3.92%
Bromhexine/Orciprenaline	Amoxicillin/Clavulanic acid	7887	2.84%
Amoxicillin/Clavulanic acid	Salbutamol	4304	1.55%
Bromhexine/Orciprenaline	Cefpodoxime	3533	1.27%
Amoxicillin	Salbutamol	2944	1.06%
Bromhexine/Orciprenaline	Amoxicillin	2789	1.00%
Theophylline/Etophylline	Erythromycin	2006	0.72%
Bromhexine/Orciprenaline	Clarithromycin	1456	0.52%
Bromhexine/Orciprenaline	Cefuroxime	1305	0.47%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

The combinations of bronchodilators and antibiotics are, therefore, rather a reflection of respiratory infections than asthma. Both age groups' combination of two products showed similar patterns and it can be concluded that amoxicillin and amoxicillin in combination with clavulanic acid are dispensed the most to children with respiratory infections.

Three products

Tables 4.70 & 4.71 illustrate the different combinations of products prescribed together to paediatric asthma patients. The cough mixtures with bronchodilator properties still had a high prevalence and were prescribed with an antibiotic. Corticosteroids also featured more in the combinations with three products. Prednisolone, which is an oral corticosteroid, is in a convenient syrup form and is suitable for paediatric patients.

Table 4.70: The top 10 combinations of three products prescribed together to children aged 0 – 4 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Number of prescriptions (N)	% Prescriptions*
Bromhexine/ Orciprenaline	Cefpodoxime	Prednisolone	431	0.26%
Bromhexine/ Orciprenaline	Betamethasone/ Dexchlorpheniramine	Cefpodoxime	372	0.23%
Fenoterol	Cefpodoxime	Prednisolone	333	0.20%
Theophylline/ Etophylline	Amoxicillin/ Clavulanic acid	Salbutamol	317	0.19%
Amoxicillin/ Clavulanic acid	Fenoterol	Prednisolone	315	0.19%
Fenoterol	Clarithromycin	Prednisolone	298	0.18%
Theophylline/ Etophylline	Amoxicillin	Salbutamol	262	0.16%
Bromhexine/ Orciprenaline	Clarithromycin	Prednisolone	257	0.16%
Theophylline/ Etophylline	Amoxicillin/ Clavulanic acid	Prednisolone	218	0.13%
Cefpodoxime	Prednisolone	Salbutamol	182	0.11%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.71: The top 10 combinations of three products prescribed together to children aged >4 ≤ 11 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Number of prescriptions (N)	% Prescriptions*
Theophylline/ Etophylline	Amoxicillin/ Clavulanic acid	Salbutamol	643	0.23%
Theophylline/ Etophylline	Amoxicillin	Salbutamol	574	0.21%
Theophylline/ Etophylline	Amoxicillin/ Clavulanic acid	Bethametsone	496	0.18%
Theophylline/ Etophylline	Amoxicillin/ Clavulanic acid	Prednisolone	435	0.16%
Theophylline/ Etophylline	Prednisone	Amoxicillin	420	0.15%
Bromhexine/ Orciprenaline	Cefpodoxime	Prednisolone	391	0.14%
Bromhexine/ Orciprenaline	Betamethasone/ Dexchlorpheniramine	Cefpodoxime	349	0.13%
Fenoterol	Clarithromycin	Prednisolone	306	0.11%
Bromhexine/ Orciprenaline	Clarithromycin	Prednisolone	298	0.11%
Fenoterol	Cefpodoxime	Prednisolone	229	0.08%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

The antibiotics that were prescribed the most frequently together with asthma products were still amoxicillin or amoxicillin and clavulanic acid. Clarithromycin was also shown to be a popular choice when prescribing other products for respiratory infections. The different paediatric age groups had very similar types of combinations prescribed to them.

Four products

Definite patterns can be observed regarding the prescribing of different combinations of products that might be beneficial to asthma patients (refer to tables 4.72 & 4.73).

The same types of products were always found on a prescription:

- A reliever or bronchodilator, such as salbutamol, ipratropium or fenoterol
- A controller, such as budesonide or montelukast
- An antibiotic, usually amoxicillin/clavulanic acid, cefpodoxime or clarithromycin
- A systemic corticosteroid, such as prednisolone, prednisone or betamethasone.

Therefore, when a child receives a prescription with four products and four different active ingredients on, it is a more serious case than a normal respiratory infection. Controllers are usually dispensed as a month's supply and are used to control the inflammatory response in the child's airways.

Table 4.72: The top 10 combinations of four products prescribed together to children aged 0 – 4 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Active ingredient 4	Number of prescriptions (N)	% Prescriptions*
Theophylline/Etophylline	Betamethasone	Amoxicillin/Clavulanic acid	Salbutamol	207	0.13%
Theophylline/Etophylline	Fenoterol	Amoxicillin/Clavulanic acid	Prednisolone	195	0.12%
Ipratropium/Salbutamol	Cefpodoxime	Prednisolone	Budesonide	153	0.09%
Theophylline/Etophylline	Prednisolone	Amoxicillin/Clavulanic acid	Salbutamol	135	0.08%
Betamethasone/ Dexchlorpheniramine	Ipratropium/Salbutamol	Cefpodoxime	Budesonide	133	0.08%
Theophylline/Etophylline	Amoxicillin/Clavulanic acid	Betamethasone	Salbutamol	82	0.05%
Amoxicillin/Clavulanic acid	Ipratropium/Salbutamol	Prednisolone	Budesonide	80	0.05%
Ipratropium/Salbutamol	Clarithromycin	Prednisolone	Budesonide	63	0.04%
Ipratropium	Cefpodoxime	Prednisolone	Budesonide	41	0.02%
Bromhexine/Orciprenaline	Clarithromycin	Prednisolone	Montelukast	30	0.02%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.73: The top 10 combinations of four products prescribed together to children aged >4 ≤ 11 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Active ingredient 4	Number of prescriptions (N)	% Prescriptions*
Theophylline/Etophylline	Prednisolone	Amoxicillin/Clavulanic acid	Salbutamol	344	0.12%
Theophylline/Etophylline	Fenoterol	Amoxicillin/Clavulanic acid	Prednisolone	222	0.08%
Theophylline/Etophylline	Betamethasone	Amoxicillin/Clavulanic acid	Salbutamol	219	0.08%
Ipratropium/Salbutamol	Cefpodoxime	Prednisolone	Budesonide	123	0.04%
Theophylline/Etophylline	Prednisone isone	Amoxicillin	Salbutamol	108	0.04%
Betamethasone/ Dexchlorpheniramine	Ipratropium/Salbutamol	Cefpodoxime	Budesonide	102	0.04%
Ipratropium/Salbutamol	Clarithromycin	Prednisolone	Budesonide	80	0.03%
Theophylline/Etophylline	Prednisone isone	Amoxicillin/Clavulanic acid	Salbutamol	75	0.03%
Amoxicillin/Clavulanic acid	Ipratropium/Salbutamol	Prednisolone	Budesonide	69	0.02%
Fenoterol	Clarithromycin	Prednisolone	Montelukast	33	0.01%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

Five products

Tables 4.74 and 4.75 provide information on combinations of five different products prescribed together to asthmatic children during the study period. The number of prescriptions become less as the number of products on the prescriptions increases. However, if these prescriptions are dispensed it indicates that the child has a severe condition. Tables 4.74 and 4.75 contain more controller medication and glucocorticoids, that are used in severe exacerbations. Fewer cough syrups were included in the combinations, which may suggest that the child rather had an asthma exacerbation or respiratory distress and developed a secondary bacterial infection, which was treated by means of an antibiotic.

Table 4.74: The top 8 combinations of five products prescribed together to children aged 0 – 4 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Active ingredient 4	Active ingredient 5	Number of prescriptions (N)	% Prescriptions*
Ipratropium/Salbutamol	Cefpodoxime	Prednisolone	Budesonide	Montelukast	15	0.009%
Bromhexine/Orciprenaline	Ipratropium/Salbutamol	Cefpodoxime	Prednisolone	Budesonide	11	0.007%
Salbutamol	Budesonide	Clarithromycin	Prednisolone	Montelukast	11	0.007%
Bromhexine/Orciprenaline	Ipratropium/Salbutamol	Prednisolone	Budesonide	Cefuroxime	9	0.005%
Amoxicillin/Clavulanic acid	Ipratropium/Salbutamol	Prednisolone	Budesonide	Montelukast	8	0.005%
Betamethasone/ Dexchlorpheniramine	Ipratropium/Salbutamol	Cefpodoxime	Budesonide	Montelukast	8	0.005%
Ipratropium	Clarithromycin	Prednisolone	Budesonide	Montelukast	7	0.004%
Beclomethasone	Fenoterol	Fluticasone	Budesonide	Montelukast	6	0.004%

* %Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (165291) and multiplying by 100.

Table 4.75: The top 8 combinations of five products prescribed together to children aged >4 ≤ 11 years from 2005 to 2008

Active ingredient 1	Active ingredient 2	Active ingredient 3	Active ingredient 4	Active ingredient 5	Number of prescriptions (N)	% Prescriptions*
Clarithromycin	Prednisolone	Fluticasone	Montelukast	Salbutamol	16	0.006%
Amoxicillin/ Clavulanic acid	Prednisolone	Fluticasone	Montelukast	Salbutamol	16	0.006%
Theophylline/ Etophylline	Fenoterol/Ipratropium	Ipratropium/Salbutamol	Amoxicillin/Clavulanic acid	Betametasone	11	0.004%
Bromhexine/ Orciprenaline	Ipratropium/Salbutamol	Cefpodoxime	Prednisolone	Budesonide	10	0.004%
Theophylline/ Etophylline	Amoxicillin/Clavulanic acid	Fenoterol	Prednisolone	Fluticasone	9	0.003%
Ipratropium/ Salbutamol	Cefpodoxime	Prednisolone	Budesonide	Montelukast	8	0.003%
Salbutamol	Amoxicillin/Clavulanic acid	Ipratropium	Fenoterol	Prednisolone	7	0.003%
Theophylline/ Etophylline	Amoxicillin/Clavulanic acid	Ipratropium/ Salbutamol	Fenoterol	Prednisolone	7	0.003%

* % Prescriptions is calculated by dividing N by the total number of asthma prescriptions in this age group from 2005 to 2008 (277480) and multiplying by 100.

Summary

By studying the information in tables 4.66 to 4.75, the most frequently prescribed antibiotics for children with asthma could be determined. Antibiotics that are used against respiratory infections were the most widely used, and probably they were used to treat a primary infection or secondary bacterial infection due to the asthma of the child. The beta-lactam antibiotics appeared to be the group that was the most frequently prescribed among paediatric patients. This group includes amoxicillin, amoxicillin/clavulanic acid and cefpodoxime that featured on the list of the most frequently prescribed combinations. Clarithromycin, which can be used in resistant bacterial infection (Rossiter, 2010:274), was also prescribed to children.

Trends regarding the prescribing patterns of systemic corticosteroids showed that prednisolone, prednisone and betamethasone were the active ingredients that were the most commonly prescribed to children. Products containing these active ingredients were convenient to use for the patients. Systemic corticosteroids should, however, only still be used in emergencies and to gain control after a severe exacerbation.

Asthma patients were found to have a higher recurrence rate of sinusitis and other respiratory infections, than patients who do not suffer from asthma (Friedman & Katsantonis, 1994:480). Therefore, the antibiotics prescribed with asthma medication have a significant occurrence.

4.7 Paediatric refill-adherence to asthma medication

The adherence of patients to their asthma medication is perceived as very poor (refer to section 2.7). Younger patients especially have a problem with adherence and it stands to reason their caregivers would have a significant influence on how and when their medication is being used. For this section the refill-adherence rate as well as other factors influencing adherence were only calculated for paediatric patients 11 years of age and younger. It was also done for the entire study period (from 2005 to 2008) and only for those products that realistic rates could be calculated for, i.e. products that come in pack sizes or doses that are enough for a month's supply. Most of these medications are controller medications and should be used on a daliy basis. The patients are also supposed to refill their prescriptions every month if they are chronic asthmatics. The refill-adherence rate was calculated per trade name only for those items that were prescribed more than once to a specific patient.

4.7.2 Refill-adherence rate

The refill-adherence rate (AR) was calculated for the products previously selected in paediatric patients. Certain limits were set to verify whether the patients were adherent or not:

- AR ≤ 90% = Unacceptable low refill-adherence rate
- 90% < AR ≤ 110% = Optimal refill-adherence rate
- AR > 110% = Unacceptable high refill-adherence rate

Table 4.76 displays the prevalence of patients in each interval of AR. Asthma patients have very poor adherence, with only 29.8% of asthma patients adhering to their medication (Bester & Hammann, 2008:20). However, the type of asthma treatment plays a role in the adherence rate, because a patient might use an inhaler for more than one month and not keep to the dose of his/her preventer medication. Therefore, it is not surprising that the largest part of patients for each product were considered non-adherent.

Controller medication and combination products were products for which the refill-adherence rate could most easily be calculated. This led to the high frequencies for some of the products. Non-adherence is the effect of many perceptions of the patient (refer to section 2.7.1). Over-adherence, in contrast, occurred when patients refilled their prescription more than 12 times per year. There could be a number of reasons for over-adherence. Patients want to keep more than one inhaler, for example one at home and one they carry around with them. They could also over-use their medication, especially in the case of bronchodilators that help during an exacerbation. According to table 4.76 the prevalence of

patients with optimal refill-adherence to their medication was not sufficient when considering asthma was classified as a chronic disease.

Patients that are not adherent to their medication or have an unacceptable low refill-adherence rate, are confronted with certain consequences. It could affect the health and well-being of the patient, lead to reduced cost-effectiveness of medical care, influence the decisions made by physicians concerning the patient's dosages and manipulate the outcomes of clinical trials of new therapies (Rapoff, 1999:10).

Table 4.76: Prevalence of paediatric asthma patients according to adherence rate from 2005 to 2008

	AR ≤ 90%		90% < AR ≤ 110%		AR > 110%	
Product	**Prevalence***	**n**	**Prevalence***	**n**	**Prevalence***	**n**
Adco Combineb® UDV	89.66%	26	3.45%	1	6.90%	2
Alvesco® 160 mcg 120D	80%	8	10%	1	10%	1
Alvesco® 160 mcg 60D	85.71%	6	14.29%	1	0	0
Alvesco® 80mcg 60D	75%	21	7.14%	2	17.86%	5
Euphyllin® retard tab	83.33%	10	0	0	16.67%	2
Flixotide® 125mcg inh	88.69%	792	7.73%	69	3.58%	32
Flixotide® 250mcg inh	79.07%	68	12.79%	11	8.14%	7
Flixotide® 25mcg inh	0	0	66.67%	2	33.33%	1
Flixotide® 50mcg inh	88.81%	238	8.58%	23	2.61%	7
Flixotide® Accuhaler 50mcg	82.09%	55	11.94%	8	5.97%	4
Flixotide® Accuhaler 100mcg	82.47%	127	13.64%	21	3.90%	6
Flixotide® Accuhaler 250mcg	82.05%	32	5.13%	2	12.82%	5
Flohale® DP caps 250mcg	20%	1	80%	4	0	0
Foratec® DP inh cap	65.79%	25	21.05%	8	13.16%	5
Foratec® 12mcg 120D inh	75%	3	25%	1	0	0
Merck Formoterol® Clickhaler	40%	2	20%	1	40%	2
Microphyllin® 125mg cap	90%	9	0	0	10%	1
Nuelin® SA 250mg tab	90%	9	10%	1	0	0
Oxis® Turbuhaler	58.33%	14	33.33%	8	8.33%	2
Sabax Combineb® UDV	72.73%	8	9.09%	1	18.18%	2
Sabax Fenoterol® UDV	88.24%	15	11.76%	2	0	0
Sandoz Theophylline® 200mg tab	77.78%	7	22.22%	2	0	0
Seretide® 25/125 inh	87.94%	1465	7.44%	124	4.62%	77
Seretide® 25/250 inh	82.23%	162	10.66%	21	7.11%	14
Seretide® 25/50 inh	86.38%	628	8.94%	65	4.68%	34
Seretide® 50/100 Accuhaler	83.99%	771	10.89%	100	5.12%	47
Seretide® 50/250 Accuhaler	83.77%	480	11.52%	66	4.71%	27
Seretide® 50/500 Accuhaler	83.33%	20	16.67%	4	0	0
Serevent® Accuhaler	65.71%	23	28.57%	10	5.71%	2
Serevent® inh 60D	76.60%	36	14.89%	7	8.51%	4
Singulair® 10mg tab	82.24%	213	14.67%	38	3.09%	8
Singulair® 4mg tab	83.61%	3071	11.65%	428	4.74%	174
Singulair® 5mg tab	85.35%	2138	10.66%	267	3.99%	100
Singulair® 4mg sprinkles	88.69%	729	6.81%	56	4.50%	37
Symbicord® 80/4.5mcg inh 120D	76.47%	13	17.65%	3	5.88%	1
Symbicord® 160/4.5mcg inh 120D	82.39%	117	8.45%	12	9.15%	13
Symbicord® 160/4.5mcg inh 60D	81.75%	103	14.29%	18	3.97%	5
Theoplus® 200mg tab	60%	6	0	0	40%	4
Uniphyl® 400mg tab	66.67%	2	0	0	33.33%	1
Uniphyl® 600mg tab	25%	1	0	0	75%	3
Zaditen® 1mg	83.87%	26	9.68%	3	6.45%	2

* AR ≤ 90%, 90% < AR ≤ 110% and AR > 110% Prevalence was calculated by adding the three frequencies of patients (n) per product together and dividing each separate n by the total multiplied by 100.

Table 4.77: Adherence rate of asthma products in paediatric patients from 2005 to 2008

Product	Average adherence rate	Frequency (N)
Adco Combineb® UDV	28.56% ± 41.00	29
Alvesco® 160mcg 120D	58.54% ± 30.98	10
Alvesco® 160mcg 60D	39.50% ± 35.86	7
Alvesco® 80mcg 60D	94.18% ± 166.11	28
Euphyllin® retard tab	54.24% ± 112.86	12
Flixotide® 125mcg inh	41.02% ± 77.22	893
Flixotide® 250mcg inh	59.54% ± 74.13	86
Flixotide® 25mcg inh	105.88% ± 16.75	3
Flixotide® 50mcg inh	45.98% ± 125.84	268
Flixotide® Accuhaler 50mcg	62.16% ± 97.80	67
Flixotide® Accuhaler 100mcg	51.40% ± 34.00	154
Flixotide® Accuhaler 250mcg	53.29% ± 36.46	39
Flohale® DP caps 100mcg	29.24% ± 17.67	4
Flohale® DP caps 250mcg	101.36% ± 7.92	5
Foratec® DP inh cap	66.00% ± 40.99	38
Foratec® 12mcg 120D inh	39.97% ± 45.64	4
Merck Formoterol® Clickhaler	91.23% ± 38.16	5
Microphyllin® 125mg cap	180.62% ± 464.46	10
Microphyllin® 250mg cap	42.12% ± 30.70	2
Nethaprin® dospan tab	6.53% ± 8.94	3
Nuelin® SA 250mg tab	41.01% ± 24.00	10
Oxis® Turbuhaler	69.64% ± 35.49	24
Sabax Combineb® UDV	67.26% ± 79.24	11
Sabax Fenoterol® UDV	31.77% ± 37.82	17
Sandoz Theophylline® 200mg tab	50.75% ± 39.11	9
Seretide® 25/125 inh	53.69% ± 175.31	1667
Seretide® 25/250 inh	67.60% ± 218.74	197
Seretide® 25/50 inh	50.54% ± 138.19	727
Seretide® 50/100 Accuhaler	54.37% ± 109.32	918
Seretide® 50/250 Accuhaler	50.79% ± 51.53	573
Seretide® 50/500 Accuhaler	47.15% ± 31.35	24
Serevent® Accuhaler	67.13% ± 38.15	35
Serevent® inh 120D	99.37% ± 332.97	79
Serevent® inh 60D	60.65% ± 30.78	32
Singulair® 10mg tab	61.13% ± 66.69	259
Singulair® 4mg tab	52.30% ± 86.17	3673
Singulair® 5mg tab	56.14% ± 140.52	2505
Singulair® 4mg sprinkles	59.67% ± 204.45	822
Symbicord® 80/4.5mcg 120D	49.79% v 39.65	17
Symbicord® 160/4.5mcg 120D	78.09% ± 298.92	142
Symbicord® 160/4.5mcg 60D	51.06% ± 41.77	126
Theoplus® 200mg tab	75.75% ± 43.98	10
Uniphyl® 400mg tab	73.59% ± 55.17	3
Uniphyl® 600mg tab	76.90% ± 45.15	4
Volmax® 4mg tab	17.28% ± 17.28	2
Zaditen® 1mg tab	83.56% ± 173.33	31
Zaditen® SRO 2mg tab	66.35% ± 12.24	2

The refill-adherence rate of the different asthma products varied according to table 4.77. The average adherence rate for all the asthma products was 60.95%, which makes the patients non-adherent. Overall it seemed that controller medicines had a better adherence rate than reliever medication. This is understandable, since most of the reliever medications should only be used as needed.

Of the 47 listed products in table 4.77, only 6 showed optimal adherence. Alvesco® 80mcg metered dose inhaler, a corticosteroid (ciclesonide), had an average refill-adherence rate of 94.18% ± 166.11 and should strictly be used for controlling asthma only. Flixotide® 25mcg inhaler and Flohale® 250mcg capsules are both fluticasone preparations, also a corticosteroid, and had adherence rates of 105.88% ± 16.75 and 101.36% ± 7.92 respectively. This means that patients on these products refilled their prescriptions more than 12 times a year and could be the result of inadequate use of medication, but not necessarily. For Singulair® tablets, which is one of the most frequently prescribed products, the refill-adherence rates for the different strengths were only average. Singulair® tablets are convenient and simple to use, as they only have to be taken once daily and are chewable. They are usually prescribed as a chronic medication to control the patient's asthma. Seretide® and Symbicord® inhalation devices, which may aid in the control and relief of asthma, also showed refill-adherence rates which were considered to be too low to be accepted as sufficient adherence.

Overall it can be said that the refill-adherence rates of certain asthma products are not satisfactory. The same conclusion was made by Bester and Hammann (2008:20). Asthma patients have many factors influencing them and causing them not to take their medication according to the instructions given to them (refer to section 2.7.1).

4.7.3 Adherence and costs

Table 4.78 displays the amounts that were spent on products that were subject to unacceptable low refill-adherence rates in paediatric patients during the study period. Some of the products are very costly and have an unacceptable low adherence rate. Unacceptable low refill-adherence to medication occurred more frequently than optimal adherence; therefore, the expenditure on medication that was not used correctly was more than it should have been.

Some of the medications, for example the Seretide® 25/125 metered dose inhaler, had an expenditure of R 2 260 400.83 in the unacceptable low refill-adherence category and made up 70.81% of the total amount spent on the product by patients that were included in the refill-adherence calculations. This is a costly product and patients are taking the risk of wasting their money, because if the product is not used correctly, the best possible control for their asthma cannot be achieved. In many cases the amounts that were spent on medication that were subject to unacceptable low refill-adherence made up 50% or more of the total amount that was spent on the medication.

The high costs asscosiated with some asthma products may have a large impact on patient non-adherence, but by not adhering to his/her treatement regimes the patient is causing the disease treatment to become even more costly. Hospitilisation costs, as well as indirect costs that have an impact on a patient's ability to work due to asthma, may be even more expensive over a longer period of time and prevent the treatment of asthma from being cost-effective to the patient (refer to section 2.7.3).

Table 4.78: The expenditure of products that were subject to unacceptable low refill-adherence rates from 2005 to 2008

Product	Cost for unacceptable low refill-adherence rate (R)	Cost per item total (R)	% Cost for unacceptable low refill-adherence*	Frequency (N)
Adco Combineb® UDV	3 646.61	6 695.18	54.47%	26
Alvesco® 160mcg 120D	9 314.32	18 899.56	49.28%	8
Alvesco® 160mcg 60D	3 872.35	7 513.87	51.54%	6
Alvesco® 80mcg 60D	15 026.73	23 724.52	63.34%	21
Euphyllin® retard tab	1 149.28	1 864.60	61.64%	10
Flixotide® 125mcg inh	696 891.80	1 033 970.34	67.40%	792
Flixotide® 250mcg inh	105 219.51	172 229.01	61.09%	68
Flixotide® 50mcg inh	100 084.80	162 483.56	61.60%	238
Flixotide® Accuhaler 50mcg	17 621.07	33 434.74	52.70%	55
Flixotide® Accuhaler 100mcg	81 517.28	129 324.56	63.03%	127
Flixotide® Accuhaler 250mcg	38 587.19	59 041.18	65.36%	32
Flixotide® Accuhaler 500mcg	1 357.68	1 697.10	80.00%	1
Flohale® DP caps 100mcg	673.4	978.38	68.83%	4
Flohale® DP caps 250mcg	396.72	3 855.21	10.29%	1
Foratec® DP inh cap	12 475.76	21 179.30	58.91%	25
Foratec® 12mcg 120D inh	311.84	1 123.53	27.76%	3
Merck Formoterol® Clickhaler	2 323.92	11 109.07	20.92%	2
Microphyllin® 125mg cap	2 729.33	4 511.81	60.49%	9
Microphyllin® 250mg cap	185.96	371.92	50.00%	2
Nethaprin® dospan tab	491.01	989.24	49.64%	3
Nuelin® SA 100mg tab	434.45	521.34	83.33%	1
Nuelin® SA 250mg tab	2 229.02	2 791.08	79.86%	9
Oxis® Turbuhaler	24 758.37	45 867.95	53.98%	14
Sabax Combineb® UDV	1 860.43	3 531.97	52.67%	8

Table 4.78 (continued): The expenditure spent on products that were subject to non-adherence rates from 2005 to 2008

Product	Cost for unacceptable low refill-adherence rate (R)	Cost per item total (R)	% Cost for unacceptable low refill-adherence*	Frequency (N)
Sabax Fenoterol® UDV	902.78	1 824.94	49.47%	15
Sandoz Theophylline® 200mg tab	495.36	1 688.89	29.33%	7
Seretide® 25/125 inh	2 260 400.83	3 192 142.95	70.81%	1465
Seretide® 25/250 inh	288 830.02	427 229.49	67.61%	162
Seretide® 25/50 inh	603 554.76	959 846.47	62.88%	628
Seretide® 50/100 Accuhaler	999 097.31	1 493 005.19	66.92%	771
Seretide® 50/250 Accuhaler	694 601.62	1 112 672.45	62.43%	480
Seretide® 50/500 Accuhaler	26 983.09	38 497.65	70.09%	20
Serevent® Accuhaler	46 878.50	88 071.31	53.23%	23
Serevent® inh 120D	70 815.69	137 301.18	51.58%	54
Serevent® inh 60D	11 409.90	25 471.80	44.79%	25
Singulair® 10mg tab	280 975.38	428 762.16	65.53%	213
Singulair® 4mg tab	3 286 102.60	5 320 025.63	61.77%	3071
Singulair® 5mg tab	3 035 802.50	4 543 062.62	66.82%	2138
Singulair® 4mg sprinkles	470 523.58	743 588.03	63.28%	729
Symbicord® 80/4.5mcg 120D	6 444.45	21 778.17	29.59%	13
Symbicord® 160/4.5mcg 120D	184 310.85	281 391.14	65.50%	117
Symbicord® 160/4.5mcg 60D	73 032.25	132 987.77	54.92%	103
Theoplus® 200mg tab	1 424.33	3 545.99	40.17%	6
Uniphyl® 400mg tab	636.66	1 145.96	55.56%	2
Uniphyl® 600mg tab	150.64	4 020.98	3.75%	1
Volmax® 4mg tab	180.96	361.92	50.00%	2
Zaditen® 1mg tab	13 553.92	25 272.09	53.63%	26
Zaditen® SRO 2mg tab	641.14	1 282.28	50.00%	2

* %Cost for unacceptable low refill-adherence rate was calculated by dividing the cost for non-adherence by the cost per item total for each product multiplied by 100.

Table 4.79: The expenditure of products that were subject to unacceptable high refill-adherence rates from 2005 to 2008

Product	Cost for unacceptable high refill-adherence rate (R)	Cost per item total (R)	%Cost for unacceptable high refill-adherence rate*	Frequency (N)
Adco Combineb® UDV	227.36	6 695.18	3.40%	2
Alvesco® 160mcg 120D	3 900.23	18 899.56	20.64%	1
Alvesco® 80mcg 60D	1 768.54	23 724.52	7.45%	5
Euphyllin® retard tab	96.81	1 864.60	5.19%	2
Flixotide® 125mcg inh	24 228.96	1 033 970.34	2.34%	32
Flixotide® 250mcg inh	5 091.81	172 229.01	2.96%	7
Flixotide® 25mcg inh	99.51	2 204.37	4.51%	1
Flixotide® 50mcg inh	2 805.78	162 483.56	1.73%	7
Flixotide® Accuhaler 50mcg	1 700.55	33 434.74	5.09%	4
Flixotide® Accuhaler 100mcg	3 090.88	129 324.56	2.39%	6
Flixotide® Accuhaler 250mcg	11 100.25	59 041.18	18.80%	5
Foratec® DP inh cap	2 336.69	21 179.30	11.03%	5
Merck Formoterol® Clickhaler	6 681.85	11 109.07	60.15%	2
Microphyllin® 125mg cap	164.95	4 511.81	3.66%	1
Oxis® Turbuhaler	684.99	45 867.95	1.49%	2
Sabax Combineb® UDV	66.08	3 531.97	1.87%	2
Seretide® 25/125 inh	113 924.73	3 192 142.95	3.57%	77
Seretide® 25/250 inh	19 406.28	427 229.49	4.54%	14
Seretide® 25/50 inh	33 427.38	959 846.47	3.48%	34
Seretide® 50/100 Accuhaler	40 875.42	1 493 005.19	2.74%	47
Seretide® 50/250 Accuhaler	55 133.87	1 112 672.45	4.96%	27
Serevent® Accuhaler	1 611.10	88 071.31	1.83%	2
Serevent® inh 120D	13 641.38	137 301.18	9.94%	9
Serevent® inh 60D	1 579.59	25 471.80	6.20%	3
Singulair® 10mg tab	4 044.77	428 762.16	0.94%	8
Singulair® 4mg tab	150 600.66	5 320 025.63	2.83%	174
Singulair® 5mg tab	131 336.66	4 543 062.62	2.89%	100
Singulair® 4mg sprinkles	19 315.51	743 588.03	2.60%	37
Symbicord® 80/4.5mcg 120D	1 855.96	21 778.17	8.52%	1
Symbicord® 160/4.5mcg 120D	19 421.36	281 391.14	6.90%	13
Symbicord® 160/4.5mcg 60D	3 975.75	132 987.77	2.99%	5
Theoplus® 200mg tab	1 340.82	3 545.99	37.81%	4
Uniphyl® 400mg tab	254.64	1 145.96	22.22%	1
Zaditen® 1mg tab	735.65	25 272.09	2.91%	2

*% Cost for unacceptable high refill-adherence rate was calculated by dividing the cost for over-adherence by the cost per item total for each product multiplied by 100.

An unacceptable high refill-adherence rate to some of the medications also occurred, but not as often as unacceptable low refill-adherence rates (refer to table 4.79). This has led to over-spending in some cases, because patients acquired more medicine than they could use in a period of one year. In the case of Singulair® 4mg tablets there were 174 patients that filled their prescription too regularly and the costs involved made up 2.83% of the total costs of this medicine item. Unacceptable high refill-adherence rates are, therefore, not recommended because the patient either did not adhere to dosage regimens or spent too much on medicine they did not use.

An unacceptable high refill-adherence rate, however, is not as serious as an unacceptable low refill-adherence rate and there could be different reasons for this occurrence. Breakages, additional inhalation devices to keep in different places or even theft have little to do with the patient's adherence and these circumstances should be considered when looking at over-adherence.

4.7.4 Total days supplied of medicine items

Table 4.80 represents the total days supplied that certain asthma medications were used by patients between 2005 and 2008. Most of these products are considered to be chronic medicine and need to be taken over long periods of time. Some patients received the same treatment for three years (1080 days) or longer, while others continued their treatment for two months only. The calculations were only done on the asthma products that were included in the refill-adherence rate calculations.

The highest frequencies of patients were observed between one month and sixty days. The more the total days supplied became, the lower the number of patients using the product became. The limitation of determining the total days supplied of medication in paediatric age groups, is that the children became older than 11 years during the four study years and were no longer classified under the paediatric age groups.

Anti-asthmatics that included inhalers, accuhalers and tablets were used for the longest periods of time. Children used Singulair® tablets for long periods of time, which could indicate that they suffered from chronic asthma. Flixotide® inhalers were also used for longer periods of time to control paediatric asthma. Combination products, such as Seretide® and Symbicord®, were suitable to use for longer time intervals and were popular choices for continuous treatment.

Table 4.80: The total number of days asthma products were supplied to patients from 2005 to 2008

	Total days supplied															
	≤ 60		> 60 ≤ 90		> 90 ≤ 120		> 120 ≤ 180		> 180 ≤ 360		> 360 ≤ 720		> 720 ≤ 1080		> 1080	
Product	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***
Adco Combineb® UDV	267	99.63	1	0.37												
Alvesco® 160mcg 120D	17	73.91	2	8.7	1	4.35			3	13.04						
Alvesco® 160mcg 60D	37	90.24	1	2.44			1	2.44	2	4.88						
Alvesco® 80mcg 60D	56	84.85	2	3.03	1	1.52	4	6.06	2	3.03	1	1.52				
Euphyllin® retard tab	62	98.41	1	1.59												
Flixotide® 125mcg inh	1579	76.39	115	5.56	84	4.06	102	4.93	124	6	48	2.32	9	0.44	6	0.29
Flixotide® 250mcg inh	199	80.89	9	3.66	7	2.85	8	3.25	17	6.91	3	1.22	2	0.81	1	0.41
Flixotide® 25mcg inh	14	93.33									1	6.67				
Flixotide® 50mcg inh	654	84.82	32	4.15	17	2.2	23	2.98	25	3.24	15	1.95	3	0.39	2	0.26
Flixotide® Accuhaler 50mcg	168	82.76	5	2.46	7	3.45	7	3.45	12	5.91	1	0.49	2	0.99	1	0.49
Flixotide® Accuhaler 100mcg	235	70.15	18	5.37	15	4.48	23	6.87	24	7.16	15	4.48	5	1.49		
Flixotide® Accuhaler 250mcg	73	72.28	4	3.96	4	3.96	8	7.92	7	6.93	3	2.97	2	1.98		
Flixotide® Accuhaler 500mcg	7	87.5					1	12.5								
Flohale® DP caps 100mcg	19	90			1	4.76	1	4.76								
Flohale® DP caps 250mcg	5	50.00	1	10.00	1	10.00	2	20.00	1	10.00						
Foratec® DP inh cap	82	76.64	2	1.87	4	3.74	11	10.28	4	3.74	3	2.8	1	0.93		
Merck Formoterol® Clickhaler	3	37.5	1	12.5			1	12.5	1	12.5	2	25				
Microphyllin® 125mg cap	36	90	2	5	1	2.5	1	2.5								
Nuelin® SA 200mg	1	50					1	50								
Nuelin® SA 250mg	77	95.06			1	1.23	1	1.23	1	1.23	1	1.23				
Oxis® Turbuhaler	55	78.57	4	5.71	1	1.43	2	2.86	5	7.14	1	1.43	2	2.86		

Table 4.80 (continued): The total number of days asthma products were supplied to patients from 2005 to 2008

	≤ 60		> 60 ≤ 90		> 90 ≤ 120		> 120 ≤ 180		> 180 ≤ 360		> 360 ≤ 720		> 720 ≤ 1080		> 1080	
Product	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***
Sabax® Fenoterol	113	96.58	1	0.85			2	1.71	1	0.85						
Sandoz Theophylline 200mg tab	80	94.12	1	1.18	1	1.18	1	1.18	1	1.18	1	1.18				
Seretide® 25/125 inh	2319	68.57	248	7.33	149	4.41	227	6.71	261	7.72	150	4.44	25	0.74	3	0.09
Seretide® 25/250 inh	417	77.94	31	5.79	22	4.11	28	5.23	25	4.67	11	2.06	1	0.19		
Seretide® 25/50 inh	1305	75.17	120	6.91	62	3.57	86	4.95	116	6.68	34	1.96	6	0.35	7	0.4
Seretide® 50/100 Accuhaler	1260	67.38	119	6.36	83	4.44	107	5.72	189	10.11	93	4.97	17	0.91	2	0.11
Seretide® 50/250 Accuhaler	801	68.46	84	7.18	47	4.02	86	7.35	96	8.21	44	3.76	9	0.77	3	0.26
Seretide® 50/500 Accuhaler	46	79.31	4	6.9	2	3.45	4	6.9	2	3.45						
Serevent® Accuhaler	56	66.67	9	10.71	2	2.38	7	8.33	4	4.76	4	4.76			2	2.38
Serevent® inh 120D	122	69.71	13	7.43	8	4.57	8	4.57	13	7.43	11	6.29				
Serevent® inh 60D	78	78.79	8	8.08	2	2.02	4	4.04	4	4.04	2	2.02	1	1.01		
Singulair® 10mg tab	599	78.4	40	5.24	26	3.4	26	3.4	41	5.37	21	2.75	9	1.18	2	0.26
Singulair® 4mg tab	7083	78.18	487	5.38	307	3.39	391	4.32	484	5.34	270	2.98	34	0.38	4	0.04
Singulair® 5mg tab	4665	75.72	314	5.1	183	2.97	302	4.9	385	6.25	245	3.98	57	0.93	10	0.16
Singulair® 4mg sprinkles	2189	87.84	90	3.61	63	2.53	61	2.45	71	2.85	18	0.72				
Symbicord® 80/4.5mcg 60D	96	90.57	5	4.72	1	0.94	2	1.89	1	0.94	1	0.94				
Symbicord® 160/4.5mcg 120D	289	78.53	21	5.71	12	3.26	16	4.35	22	5.98	5	1.36	3	0.82		
Symbicord® 160/4.5mcg 60D	339	83.7	9	2.22	9	2.22	18	4.44	17	4.2	12	2.96	1	0.25		
Theoplus® 200mg tab	56	88.89	2	3.17			3	4.76	2	3.17						
Uniphyl® 400mg tab	57	96.61	1	1.69					1	1.69						
Uniphyl® 600mg tab	14	87.5							1	6.25	1	6.25				
Zaditen® 1mg tab	74	83.15	7	7.87	2	2.25	2	2.25	4	4.49						

* % was calculated by dividing n for each product from each interval by the total n for the product for the entire period and multiplying by 100.

4.8 Chapter summary

This chapter discussed the data that were provided by the medical claims database. From the data several aspects of paediatric asthma were evaluated and interpreted. The total database was compared to the data that involved asthma medication, and this showed the prevalence of asthma in the total population that claimed their prescriptions from the medical claims database. Paediatric asthma and its prevalence in several categories were determined. The highest ranked active ingredients and trade names in asthma medication were discussed. Furthermore, the combinations in which asthma medications were prescribed with each other could be established, as well as with antibiotics and systemic corticosteroids. Refill-adherence is an important aspect of the treatment of asthma and the refill-adherence rates and the amount of medication that patients used could be extracted from the database for a certain group of products.

In the next chapter conclusions will be drawn from the data that were discussed. The objectives that were set for this study will be considered and conclusions will be drawn in conjunction with these research objectives.

CHAPTER 5

Conclusions and recommendations

5.1 Introduction

Conclusions regarding the literature study and the results obtained from the empirical research study in chapter 4 will be discussed in this chapter. The limitations of the study will be declared and some recommendations will be made to aid in further studies regarding asthma.

5.2 Conclusions

The conclusions were drawn based on the specific objectives that were set for this study. The conclusions are, therefore, divided into two groups namely:

- Literature study conclusions
- Empirical research study conclusions

5.2.1 Literature study conclusions

- The **first research objective** was to describe and define asthma, the different types of asthma, its diagnosis and treatment guidelines.

Asthma is a complex chronic respiratory disease that is typified by frequent attacks of breathlessness and wheezing. It has variable and recurring symptoms, including airflow obstruction and bronchial hyper responsiveness. Bronchoconstriction occurs in reaction to stimuli and bronchodilation will manifest when treatment is administered (refer to section 2.2).

The diagnosis of asthma is difficult. There are differing diagnoses for asthma and diagnosis in children are especially difficult. Asthma is often over- or under-diagnosed and care must be taken to confirm that the child does truly have asthma. Diagnostic tests are available, such as measuring the peak flow expiratory rate and spirometry. Asthma can also be classified into different types, namely allergic, non-allergic, exercise induced, occupational and nocturnal (refer to section 2.3).

Asthma medications are classified into two main groups:

- Bronchodilators
- Anti-asthmatics

The bronchodilators help with quick relief in case of an exacerbation or attack. Drugs in this group include sympathomimetic agents, methylxanthines and anticholinergic agents. They are also known as “relievers”. The anti-asthmatics are also known as “controllers” or “preventers”. These drugs are taken daily to control persistent asthma, prevent attacks and to reduce airway inflammation. Drugs in these groups are the corticosteroids, leukotriene receptor antagonists and chromones (refer to section 2.5).

The NHLBI compiled guidelines for the treatment of asthma in children aged 0 – 4 years and 5 – 11 years (refer to section 2.4). A stepwise approach must be followed and the severity of the asthma must be assessed. The stepwise approach assists the clinician in deciding what the best treatment for a patient will be, but must only be used to help identify the individual patient’s needs and not replace the process of decision making on the clinician’s part.

- The **second research objective** was to describe the prevalence of asthma and according to demographical factors such as age, gender and geographical area in South Africa and other countries.

The WHO calculated that approximately 300 million people globally suffer from asthma (WHO, 2008). This disease is, however, still being under-diagnosed and under-treated and leads to many deaths annually (refer to section 1.3 & 2.6). In South Africa asthma has a significant prevalence and creates a heavy burden on patients. According to a study done by Bradshaw *et al.* (2007), asthma is eighth on the list of causes of disease burden in South Africa. The only other chronic disease that creates a greater burden is HIV/AIDS. South Africa’s asthma prevalence is ranked 25th globally with 8.1% of the population presenting with asthma symptoms (Masoli *et al.,* 2004:9). Southern Africa has a higher prevalence of asthma than the rest of Africa (Masoli *et al*., 2004:115). In South Africa specifically the risk of asthma due to occupational hazards from the mines are increasing as well (Wjst & Boakye, 2007:e72). After pneumonia and gastroenteritis, asthma is the third leading cause for hospitalisations in South Africa, especially in children (Masoli *et al*., 2004:115).

Asthma is currently the most common chronic disease in children worldwide and in South Africa the prevalence of asthma in children ranges from 10% to 20% (refer to section 2.6.3). In the United States an estimated 7.1 million children under the age of 18 years suffer from asthma and 4.1 million of them experienced an asthma attack in 2006 (American Lung Association, 2010). Tobacco smoke has a significant influence on childhood asthma. If the child’s caregiver is a smoker, the child will experience more asthma attacks. Therefore, by reducing the exposure the patient has with tobacco smoke, the morbidity of asthma might be reduced (refer to section 2.6.3).

The neighbourhood in which a patient lives can be a contributing factor to whether or not a patient develops asthma. Studies have shown that there are links between the exposure of pollutants and overall respiratory health in children (refer to section 2.6.4). Urbanisation and pollutants as a result of urbanisation are some of the factors that have an influence on the prevalence of asthma. If urbanisation continues at its current rate, the prevalence of asthma will increase considerably and by 2025 approximately 400 million people will be affected globally (Masoli *et al*., 2004:1) (refer to section 2.6.4).

In general, studies have shown that the female sex is a risk factor for developing asthma. In children, however, that is not the case. Before puberty the prevalence of asthma is much higher in boys than in girls (refer to section 2.6.5).

- The **third research objective** was to determine patients' adherence to their asthma medication as well as the economic burden that asthma has on patients.

Patient's adherence to their asthma medication is an important part of asthma therapy and whether the disease is under control. Patients that suffer from a chronic condition have lower adherence to their medication than patients that are only receiving acute treatment and this is true in the case of asthma as well. According to Bester and Hammann (2008:21) asthma has the second worst compliance out of the 27 diseases on the Chronic Disease List (CDL). Only 29.8% of patients with asthma were adherent to their medication in 2007. Patients with asthma also seem not to persist with their asthma medication over longer periods of time, with 61.5% of asthmatics persisting with their therapy for 12 months or longer. Patients that admitted to non-adherence with their asthma medication experienced worse morbidity (refer to section 2.7).

There could be a number of reasons for patient non-adherence and each case is unique. Some of the factors that may contribute to non-adherence to asthma medication include the following (refer to section 2.7.1):

- Patients not understanding the importance of controller medication
- Incorrect inhaler technique
- Dosage intervals of more than once a day
- Side-effects of medication and patients' misconceptions relating to side-effects
- The patient's attitude towards taking the medication
- The patient's age

Paediatric adherence depends on the involvement of the child's caregiver and his/her commitment to adhere to the child's asthma treatment (Osterberg & Blaschke, 2005:494). Children with asthma that receive help and positive influences from their parents or caregivers to use their controller medication, tend to be more adherent to their therapy. Children are not always able to understand why and how they should use their medication, therefore, it is important for the caregiver to explain this to the child. Older children are sometimes left in control of their own daily doses, but the caregiver should be aware if the child is in fact using the medication. Children will occasionally skip a dose to experiment with the efficacy of their medication or to avoid the embarrassment of using an inhaler where others are present. Paediatric adherence is a complicated part of asthma therapy. By monitoring the adherence to asthma medication a child may experience fewer exacerbations and less absenteeism from school because of the hindrances of asthma. This could lead to an improvement in the quality of life of the patients (refer to section 2.7.2).

Asthma is a disease that heavily burdens its patients. The patients are restrained economically, because of the costs of medicine, hospitalisation and other medical costs, but also physically and emotionally as it has an effect on their quality of life. The total expenditure for asthma in the United States is estimated to be between $12 and $14 billion and in Australia it is between $720 and $800 million annually (Edwards, 2004:60). In children asthma is currently one of the leading causes of hospitilisation and school absenteeism according to the American Lung Association (2010). Patient adherence and costs are connected. If the patient chooses to adhere to dosing regimens to keep his/her asthma under control, the expenditure of emergency room and hospital visits would be less. In this way asthma medication could become cost-effective to the patient.

5.2.2 Empirical research study conclusions

- The **first research objective** was to determine the prevalence of asthma in a section of the private health care sector of South Africa according to various demographical factors such as age and gender.

Asthma has a significant prevalence among patients in this section of the private health care sector. Although the number of patients that used asthma products decreased from 2005 (n=347342) to 2008 (n=240854), the prevalence of asthma increased from 23.01% to 24.72% as a percentage of the total number of patients on the total database (refer to table 4.2). However, when looking at the prevalence of the number of prescriptions and number of medicine items dispensed, there was a decrease from 2005 to 2008 on the total database. The number of prescriptions per patient per year showed a steady increase on the total database. The increase according to the asthma database shows that patients were claiming more prescriptions with asthma medication on per year, from 1.85 ± 2.20 prescriptions in

2005 to 2.01 ± 2.47 in 2008. On average a patient received 2 or 3 prescriptions per year for asthma medication (refer to table 4.4). If a patient is a chronic asthmatic though, this is a worrying average, because asthma sufferers should refill their prescription at least 10 times per year in order to be adherent (Bester & Hammann, 2008:20). Regarding the number of medicine items that appear on a prescription, the total database shows that there are on average 2 or 3 items on a prescription. The asthma database, however, indicates an average of 1 or 2 items per prescription that appear in MIMS pharmacological groups 10.2 or 10.4.

Overall it can be seen that the prevalence for the number of patients with asthma is highest among children between the ages of 0 and 4 years (refer to table 4.6). In 2008 the prevalence of asthma among patients aged 0 – 4 years was 44.40%. This means that almost half of the total database's patients that were between 0 and 4 years of age used medications that were in MIMS pharmacological groups 10.2 or 10.4. In the >4 ≤ 11 years age group, the prevalence of asthma patients was 32.84% in 2008. This confirms that asthma is a very prevalent disease among children in South Africa.

There were more female than male patients on the total database, but when comparing the prevalence of asthma among both genders, males seemed to have a higher prevalence when it came to the number of asthma patients, prescriptions and medicine items (refer to table 4.7). Male patients had a prevalence of 25.03% and female patients a prevalence of 24.46% in 2008. This contradicts the studies that stated that being female is a significant risk factor for asthma and, therefore, females would have a higher prevalence of asthma (refer to section 2.6.5).

Asthma is, therefore, a prevalent disease in this section of the private health care sector of South Africa. The age and gender of the patients seemed to have an influence on the prevalence of asthma, as young children and males came out as possible risk factors.

- The **second research objective** was to determine the prescribing patterns and cost of asthma medication according to therapeutic category and active ingredient.

Asthma medication expenditure was expressed as a percentage of the medicine expenditure of the total database. It was found that asthma medication represented 4.64% of the total medication expenditure in 2005 (refer to table 4.3). There was, however a decrease in the total and asthma expenditure and in 2008 asthma medication represented 4.15% of the total medication expenditure. The reason for the decrease is not clear, but it may be due to the overall decrease in medication expenditure or the decrease in the number of asthma medicine items that were dispensed. Another reason might be that more generic products were being developed and some might have been implemented during the study period. This could cause the cost of the medicine items to be reduced and, thus, would decrease the

expenditure of asthma medications. This aspect of the costs of medicine and especially asthma medicine should be investigated further to obtain an accurate cause for the decrease in medicine expenditure.

Asthma medication can be classified into different sub-groups and from these groups certain trends in the prescribing patterns can be identified. Firstly the medication was divided into therapeutic categories. According to the MIMS® classification system and the data obtained from the medical claims database the categories are indicated as listed below:

Bronchodilators (Group 10.2):

- Sympathomimetics (10.2.1)
- Methylxanthines (10.2.2)
- Anticholinergics (10.2.3)
- Combination products (10.2.4)

Anti-asthmatics (Group 10.4):

- Glucocorticoids (10.4.1)
- Leukotriene receptor antagonists (10.4.2)
- Other anti-asthmatics (Ketotifen) (10.4.4)

Combination products and methylxanthines were the most frequently prescribed therapeutic groups among patients using asthma medication (refer to table 4.9). The prevalence of these two groups increased from 2005 to 2008. A number of cough mixtures were, however, included in these groups, thus the results might not indicate the usage of products specifically in asthma. An interesting trend observed, was that leukotriene receptor antagonists appeared to be the only other group that showed an increase in usage from 2005 to 2008 (refer to table 4.10). This indicated that leukotirene receptor antagonists, although a fairly new group, are being utilised more frequently. The other therapeutic groups all showed a decrease in usage from 2005 to 2008. This may be due to the implementation of the combination products, that often included a bronchodilator and a glucocorticoid, that are more convenient to use for the patient. Patients use bronchodilators a great deal more than anti-asthmatics (refer to table 4.8). This is troublesome, because patients should in reality use their bronchodilator only when necessary and their controller medication every day. Another aspect, however, is that the ratio of bronchodilator versus anti-asthmatic medication usage in asthma patients decreased from 2005 to 2008. This can be seen as a positive sign, because patients are using their controller medication more often, but the

negative side is that patients are using more controller medication, which means that more patients are experiencing trouble with asthma and need to use chronic controller medication.

When observing the most frequently prescribed active ingredients used in asthma from 2005 to 2008, it is clear that patients used bronchodilators the most frequently. The top 5 bronchodilator products stayed the same throughout the study period (refer to tables 4.11 – 4.14). The cough mixtures were still prevalent and it is not clear whether patients truly used the products for their bronchodilator properties or not. The anti-asthmatics also showed no changes in the rankings from 2005 to 2008 (refer to table 4.16 – 4.19). Budesonide was the preferred anti-asthmatic to prescribe for asthma control from 2005 to 2008, although its prevalence decreased during this study period. Montelukast was the second most prescribed product every year and overall its prevalence increased by 12.59%. This is of importance when looking at the paediatric prescribing patterns.

- The **third research objective** was to determine the prevalence of asthma in children according to gender and geographical area in a section of the private health care sector.

According to the second literature objective (refer to section 5.2.1) the prevalence of asthma among the different genders has a definite trend. Asthma is more prevalent in males up to the age of 12 years, whereafter, females present with a higher prevalence. The data in table 4.25 prove that it is not the case in this section of the private health care sector of South Africa. Throughout the study period, males had a higher prevalence of asthma. However, the difference in prevalence is smaller in the > 11 years age group, than in the paediatric age groups. When observing the two paediatric age groups, there were no significant differences in the prevalence of asthma, except that the younger age group had a much higher prevalence than the older age group when it came to the number of patients. Regarding asthma medicine items, male patients received more items than female patients in both age groups, however, both genders showed a steady increase in prevalence.

Asthma prevalence among children differed between the provinces. The literature suggested that children in urbanised areas, where they are exposed to pollutants, experienced asthma attacks more often (refer to section 2.6.4). In South Africa, however, Limpopo, North West, Free State, Mpumalanga and the Northern Cape were always among the provinces with the highest prevalence of paediatric asthma patients (refer to table 4.35 – 4.38). By the end of 2008 Mpumalanga had the highest prevalence of asthma in the 0 – 4 years age group (36.39%), followed closely by the Free State (36.33%). In the >4 ≤ 11 years age group the Northern Cape and Limpopo had the highest prevalence of asthma of 30.43% and 29.56% respectively. These are not necessarily the provinces with most pollutants and large parts of these provinces are not urbanised. The investigation of asthma prevalence then led to the areas where mines were found in South Africa. All the provinces that have a significant

number of mines namely, Gauteng, Mpumalanga, Limpopo, Free State, North West and Northern Cape have a higher prevalence of asthma than those provinces that do not have any specific or major mining facilities or activities (InfoMine, 2010). The provinces without mines, namely the Western Cape, Kwazulu Natal and the Eastern Cape have a lower prevalence than the other provinces (refer to tables 4.35 – 4.38). A province's annual precipitation does not seem to have an influence on childhood asthma, since the Western Cape has the lowest prevalence of asthma (refer to table 4.35 – 4.38), but is also the province with the second lowest mean annual precipitation (Breedlove & Jordaan, 2001).

This correlates with the trends found in literature study. Urbanised areas should have a higher asthma prevalence than rural areas, but it is difficult to be sure of the South African situation, because pollutants may be found in rural as well as urbanised areas, due to mining and smoke. More extensive studies should be done to determine the causes of asthma in urbanised and rural areas.

- The **fourth research objective** was to determine the costs associated with paediatric asthma medication.

Asthma is a costly disease for the patients involved worldwide. For this reason the total expenditure of the disease had to be determined. The percentage that asthma costs represent as part of the total database (refer to table 4.24) is much higher in the paediatric age groups than in the total asthma population (refer to table 4.3). Asthma expenditure represented 11.63% of the total expenditure in children aged 0 – 4 years in 2005. It increased by 4.08% to 15.71% in 2008. In the >4 ≤ 11 years age group it increased by 4.20% from 2005 (12.55%) to 2008 (16.75%). This indicates that asthma medication is being used more often in the paediatric age groups and that asthma has a significant part to play in the total health expenditure of the medical claims database. The asthma expenditure in this study was concerned with the cost of medication used to treat asthma only. Hospitalisation and other tangible costs, which play an important role in the overall costs of asthma, were not included but could be useful in further studies (refer to section 5.4).

- The **fifth research objective** was to investigate the prescribing patterns of asthma medication to paediatric patients according to therapeutic category, active ingredient, trade name and prescriber.

The prescribing patterns of asthma medication to paediatric patients were slightly different if compared to the total study population. When observing the ratio of prescribed bronchodilators to anti-asthmatics, a more favourable result was seen (refer to tables 4.8 & 4.40 & 4.41). The ratio was lower in both paediatric age groups than in the total study

population. This means that paediatric patients received more controller medications than the rest of the patients on the asthma database.

The increases and decreases in the usage of the different therapeutic categories varied in the two paediatric age groups (refer to table 4.43). Glucocorticoids were being used less in the > 4 ≤ 11 years age group, than in the 0 – 4 years age group, while anticholinergics were being used more in the older than in the younger age group (refer to table 4.42). This may be due to the fact that anticholinergic drugs quickly precipitate toxic effects in young children and are currently being phased out as an effective treatment (Rossiter, 2010:542). Leukotriene receptor antagonists showed a large increase in both the > 4 ≤ 11 years and the 0 – 4 years age groups of 9.12% and 7.59% respectively from 2005 to 2008 (refer to table 4.42).

The top 5 bronchodilator active ingredients remained the same throughout the study period for the 0 – 4 years age group (refer to table 4.44). These products were: bromhexine/orciprenaline, salbutamol, theophylline/etophylline, fenoterol and ipratropium/salbutamol. Combination products were popular among this age group, but once again the cough mixtures were included in this data. The top 5 active ingredients in the 0 – 4 years and > 4 ≤ 11 years age groups were very similar (refer to tables 4.44 & 4.45). Salmeterol/fluticasone played a bigger part in the prescribed medicine items for the > 4 ≤ 11 years age group.

The anti-asthmatics showed interesting trends when looking at the most frequently prescribed active ingredients. When looking at table 4.46, there is a clear front-runner in the anti-asthmatic category among children aged 0 – 4 years. Montelukast, the most well-known leukotriene receptor antagonist, was the active ingredient that was prescribed most frequently. From 2005 (n=4803) to 2008 (n=4543) it showed an increase of 19.08% and comprised 56.46% of all anti-asthmatic prescriptions in this age group by the end of 2008. Budesonide, the most prescribed corticosteroid, in contrast showed a decrease as it started being used less often as the preventer medication of choice. By the end of 2008 its prevalence stood at 29.81%. In the > 4 ≤ 11 years age group montelukast and budesonide also dominated as the most frequently prescribed anti-asthmatics (refer to table 4.47). Montelukast made up 52.24% of anti-asthmatic prescriptions in this age group in 2008. Its prevalence also had a sudden increase, as was seen in the 0 – 4 years age group (refer to table 4.46). Budesonide was prescribed the most in 2005, when it made up 34.93% of the anti-asthmatic medicine items.

The top 4 trade names used by paediatric asthma patients in both age groups were the same from 2005 to 2008 (refer to tables 4.48 – 4.55). These products were Alcophyllex®, Singulair®, Venteze® syrup and Adco-Linctopent®. Alcophyllex® (12.49% in 2008) was the

product that was the most frequently prescribed to the > 4 ≤ 11 years age group. In children aged 0 – 4 years, however, Singulair® 4mg tabs (11.56%) managed to surpass Alcophyllex® (9.35%) in 2008, to be the most frequently prescribed trade name. This correlates with the prescribing patterns of the anti-asthmatic active ingredients, which indicated that montelukast (Singulair®) was the most frequently prescribed active ingredient (refer to table 4.46).

The general trend seen in the prescribing patterns of the different prescribers is that general practitioners are becoming less involved in the treatment of paediatric asthma and the prevalence of their prescriptions decreased from 2005 to 2008 and more parents would rather take their child to a paediatrician for asthma medication prescriptions. In the 0 - 4 years age group general practitioners were consulted the most often, but paediatricians also had a presence among the prescribers (refer to tables 4.26 – 4.29). In the older age group, > 4 ≤ 11 years, the same trend as in the younger age group was displayed with regard to the general practitioners and paediatricians. The prevalence of the general practitioners in the > 4 ≤ 11 years age group was, however higher than in the 0 - 4 years age group. Pulmonologists had the lowest prevalence of all the prescribers that were involved in the prescribing of asthma medication to young children.

The number of items prescribed by the different prescribers are of interest. In the 0 – 4 years and > 4 ≤ 11 years age groups certain trends were observed. Pulmonologists prescribed the most items per prescription on average from 2005 to 2008, but they also prescribed the lowest number of items of all the prescribers (refer to tables 4.31 & 4.32). Paediatricians' and general practitioners' number of items per prescription showed an increase from 2005 to 2008. Paediatricians averaged between 1 or 2 items per prescription from 2005 to 2008. General practitioners were most often consulted and prescribed the most items, but had a lower average of number of items per prescription than paediatricians (refer to tables 4.31 & 4.32). When examining the costs of the different prescribers' prescriptions in the different age groups it can be said that children in the older age group were written more expensive prescriptions by general practitioners and paediatricians, but the differences were not significant according to *d*-values (0.11 and 0.23 respectively in 2008). On average, paediatricians' prescriptions were more expensive than those of the general practitioners in the 0 – 4 years age group (*d*-value of 0.65 in 2008) and the > 4 ≤ 11 years age group (*d*-value of 0.79 in 2008) and other health specialists from 2005 to 2008 and the average cost per prescriptions written by paediatricians only increased (refer to table 4.33 & 4.34).

This research objective was reached by studying all the active ingredients and trade names of the medications in groups 10.2 and 10.4 of the MIMS classification. Only the top 20 trade names were displayed due to the number of trade names available in these groups (refer to tables 4.48 – 4.55). The prescribers and their different prescribing patterns were also

investigated and it was determined that specialists prescribe slightly more medicine items per prescription and had a slightly higher cost per prescription than general practitioners.

- The **sixth research objective** was to review the prevalence of the prescribing of antibiotics and/or systemic corticosteroids together with asthma therapy.

Children with asthma often receive other medications because of their asthma (refer to section 2.5.5). The most frequently prescribed antibiotics in the paediatric age groups can be seen in tables 4.62 & 4.63. Amoxicillin/clavulanic acid was the antibiotic that was prescribed the most to children using medication from groups 10.2 and 10.4. In tables 4.64 and 4.65 the most frequently prescribed corticosteroids to these patients are presented. Prednisolone was the corticosteroid that was used the most often to bring severe asthma exacerbations under control. Antibiotics that were used against respiratory infections were the most widely used, regardless of whether they were used to treat a primary infection or secondary bacterial infection due to the asthma of the child. The beta-lactam antibiotics formed the group that was the most frequently prescribed among paediatric patients. Trends regarding the prescribing patterns of systemic corticosteroids showed that prednisolone, prednisone and betamethasone were the active ingredients that were the most commonly prescribed to children (refer to tables 4.66 – 4.75). The usage of antibiotics is an indication of a secondary infection and the use of corticosteroids usually indicates that a child had a severe exacerbation and that the asthma had to be brought under control. The more products a child used, the more severe the condition was thought to be. This is because cough syrups were not as prevalent in the combinations of four or more products and the child usually received controller medication.

Combinations of asthma medication and antibiotics and systemic corticosteroids may have different indications for each patient, but most of the combinations of medication would refer to a respiratory infection (Department of Health, 2008:280). Asthma patients were found to have a higher recurrence rate of sinusitis and other respiratory infections, than patients who did not suffer from asthma (Friedman & Katsantonis, 1994:480). Therefore, the antibiotics prescribed with asthma medication have a significant occurrence.

- The **seventh research objective** was to investigate the paediatric patients' refill-adherence rate to certain asthma medication.

The adherence of asthma patients is notoriously poor as many studies have proved (refer to section 2.7). This research objective, therefore, aimed to calculate what the refill-adherence rate among patients in South Africa would appear to be. It was to be expected that paediatric patient refill-adherence would not be optimal.

The refill-adherence rate for the products that were brought into consideration was not satisfactory (refer to table 4.77). A large majority of the products had a refill-adherence rate of below 90%, which meant that they had an unacceptable low refill-adherence rate. The mean adherence rate for all the asthma products was 60.95%, which is sub-standard (refer to section 4.7.1).

According to table 4.76 the prevalence of patients that showed an optimal refill-adherence rate to their medication was not sufficient when considering that asthma has been classified as a chronic disease. The majority of patients had an unacceptable low refill-adherence rate.

Table 4.78 displays the amounts that were spent on products that were subject to unacceptable low-adherence rates in paediatric patients during the study period. Some of the products are very costly and have an unacceptable low refill-adherence rate for the amount the patients are paying. Unacceptable low refill-adherence rates to medication were more frequent than optimal refill-adherence rates; therefore, the expenditure on medication that was not used correctly was more than it should have been.

Unacceptable high refill-adherence rates to some of the medications also occurred, but not as often as unacceptable low refill-adherence rates (refer to table 4.79). This has led to over-spending in some cases, because the patients acquired more medicine than they could use in a period of one year. Unacceptable high refill-adherence rates are, therefore, not recommended because the patient either did not adhere to dosage regimens or spent too much on medicine they did not use.

The total days that a medicine was supplied to a patient, should indicate whether a patient used his/her medication on a long-term basis or whether the medicine was merely dispensed for an acute episode. Most patients did not use their asthma medication for very long periods of time (refer to table 4.80). The highest frequencies of patients were observed at less than sixty days. The more the total days supplied became, the fewer the number of patients using the product become. Very few patients continued with their therapy for a year (360 days) or longer.

It can therefore be confirmed that the refill-adherence rate for paediatric patients in South Africa is not ideal and that there should be more careful monitoring of the patient, considering that the patients involved in this study are still children. Physicians should also be more involved in the education of the patients about the importance of refill-adherence.

5.3 Limitations of the study

There were several limitations that had an influence on the study and the accuracy thereof. The following limitations should be taken into account:

- The data for analysis were obtained from one medicine claims database only, therefore external accuracy is limited and the results can only be generalised to the allocated database and study population that were used in this study.
- All data entered into the database were considered to be correct and the data were analysed from this perspective.
- Numerical values were rounded off to two decimal places.
- The database did not contain the diagnosis (ICD10-code) of the patient or the patient's medical history.
- The clinical outcomes of the patients with different refill-adherence rates could not be determined, because the necessary information was not available from the medical claims database.
- Cough mixtures were brought into account when classifying the medications as "bronchodilators". Therefore, completely accurate findings could not be made, as many patients receive cough medicine on a daily basis that is not necessarily linked to asthma.
- Hospitilisation costs were not available from the database, therefore, the monetary medical burden of asthma could not be determined completely.

5.4 Recommendations

- The geographic distribution of asthma patients should be further investigated. The environmental factors should then be considered as a basis for the prevalence of asthma in the specific locations.
- The clinical diagnosis should be identified by using ICD-10 codes to determine whether the patient has asthma or another respiratory condition.
- The patient refill-adherence rate could be more accurately determined by considering whether the prescription was authorised by the medical claims database as chronic, acute or prescribed minimum benefit (PMB) medication. The financial implications of non-adherence should also be investigated.
- The hospitalisation costs must be obtained in order to accurately determine the direct medical costs of asthma. Further studies involving indirect costs and the quality of life of patients can also be undertaken.

- Since more generic equivalents are becoming available for the expensive asthma medications, studies involving cost-effectiveness and cost-minimisation could be carried out.

- The prevalence of asthma should constantly be monitored. The prevalence of asthma in young adolescents is an area of research that could be investigated, especially since there are some emotional factors that have an impact when dealing with a chronic disease in adolescents.

- Patients could be monitored over a longer study period and by giving each patient a unique number and monitoring that patient's progress in the treatment of his/her asthma, more accurate findings will be obtained.

5.5 Chapter summary

In this chapter the conclusions that were drawn from the literature and empirical research study were discussed. Some limitations involved in the study were mentioned and recommendations were made to aid future studies regarding asthma and its treatment in South Africa.

CHAPTER 6

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