

A LONGITUDINAL STUDY OF THE USAGE OF ACID REDUCING MEDICINE USING A MEDICINE CLAIMS DATABASE.

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B.Pharm

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This dissertation is dedicated in memory to my father, who has consistently loved, encouraged
and supported me.

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ABSTRACT

Title: A longitudinal study of the usage of acid reducing medicine using a medicine claims database.

Keywords: Acid-related disorders, dyspepsia, peptic ulcer disease (PUD), gastro-oesophageal reflux disease (GORD), Zollinger-Ellison syndrome, acid reducing medicine, histamine-2 receptor antagonists (H₂RAs), proton pump inhibitors (PPIs), managed care, pharmaco-economics, drug utilisation review, single exit price (SEP), generic, innovator, prevalence, cost and prescribed daily dose (PDD).

Acid-related disorders are common, chronic conditions that have considerable impact on a patient's quality of life. In a study conducted by Majumdar *et al.* (2003:2411) the prevalence of chronic acid-related disorders was 2.3%. Acid-related disorders represent a major financial consideration with respect to the costs of drug prescribing (Whitaker, 1998:6). Health care cost increases each year. This leads to an increased interest in economic evaluation of health care and medical technologies (Anell & Svarvar, 2000:175). Health care providers no longer make treatment decisions independent of the consideration of the resultant cost. The treatment provided must not only provide value but the value must be documented to justify spending money. Economic evaluation research has emerged to offer guidance to policy makers, practitioners, health plans and institutions facing difficult treatment and coverage decisions (Ellis *et al.*, 2002:271).

The main objectives of this study were to investigate the prescribing patterns and cost of acid reducing medicine with special reference to proton pump inhibitors and histamine-2 receptor antagonists in a section of the private health care sector of South Africa from 2001 to 2006. A longitudinal retrospective drug utilisation study was done on acid reducing medicine items claimed through a national medicine claims database. The five study years were 2001, 2002, 2004, 2005 and 2006. All the study years stretched from 1 January to 31 December.

It was determined that acid reducing medicine items prescribed decreased from 2.74% during 2001 to 2.50% during 2006 of all medicine items claimed. The same decreasing trend was observed regarding the cost of acid reducing medicine items. The cost percentage decreased from 4.89% (2001) to 3.72% (2006). However, the average cost per medicine item for the acid reducers increased by 5.35% from 2001 (R230.04 ± 176.29) to 2002 (R243.72 ± 184.18) and then decreased by 15.23% from 2002 to 2004. It again decreased with 15.05% from 2004

(R206.19 ± 179.42) to 2006 (R175.70 ± 172.55). The changes in the average cost of acid reducers were of no practical significance.

Proton pump inhibitors represented about half of the acid reducing medicine items prescribed and more than 70% of the total cost of acid reducing medicine items during the study years. The average cost of PPIs revealed a practical significant decrease ($d > 0.8$) from 2002 (R372.42 ± 156.62) to 2006 (R241.56 ± 177.21). H₂RAs contributed between 15.00% and 18.26% of all acid reducing medicine items while contributing to between 9.68% and 16.85% of the total cost of all acid reducers.

The active ingredient most often prescribed was lansoprazole during 2001 and 2002, esomeprazole during 2004 and omeprazole during 2005 and 2006. Lanzor® 30mg was the acid reducer with the highest cost from 2001 to 2005, while Pariet® 20mg took the lead in 2006. Zantac® 150mg effervescent tablets were the H₂RA, with the highest cost, during the five study years.

The percentage innovator items decreased by 4.50% from 2001 to 2002, increased by 1.01% from 2002 to 2004 and decreased again by 31.06% from 2004 to 2006. The slight increase in the percentage innovator medicine items claimed from 2002 to 2004 may be explained by the introduction of Nexiam® (esomeprazole) into the market in 2002. The total number of generic medicine items claimed contributed between 9.62% ($n = R1\ 788\ 242.25$) in 2001 and 30.75% ($n = R3\ 196\ 163.34$) in 2006 of the total cost of acid reducing medicine items.

The average cost per day of innovator medicine items was higher than the average cost per day of generic medicine items. This might be explained by a lower average cost for generic medicine items.

It was also determined that the prevalence of the two-drug regimens was the highest during the five study years. The *Helicobacter pylori* (*H.pylori*) eradication treatments, which included different antibiotics, increased from 2.72% in 2001 to 5.05% in 2006.

The PDD for most of the active ingredients of H₂RAs and PPIs remained stable during the study years. However, it appears that the PDDs, of the PPIs, active ingredients were more constant than the PDDs, or the H₂RAs, active ingredients. The median of the different PPI active ingredients was reasonably more constant than the median of the different H₂RA active ingredients. Thus the changes between the PPIs' and H₂RAs' active ingredients might be explained by the variation in the median (the number of days the relevant medicine item was claimed for).

It is then also recommended that the aspects of generic substitution as well as the usage of H₂RAs as prescribed vs. self medication should be further investigated to increase possible cost savings.

OPSOMMING

Titel: 'n Longitudinale studie met behulp van 'n medisyne-eisedatabasis van die gebruik van teensuurmedikasie

Sleutelwoorde: Suurverwante siektes, dispepsie, peptiese ulkussiekte, gastroësofagiale reflukssiekte, Zollinger-Ellisonsindroom, teensuurmedikasie, histamien-2-reseptorantagoniste (H₂RA's), protonpompremmers (PPR's), bestuurde gesondheidsorg, farmako-ekonomie, medisyneverbruiksevaluering, enkeluitgangsprys, generies, innoveerder, voorkoms, koste en voorgeskrewe daaglikse dosis

Suurverwante siektes is algemene, kroniese siektetoestande wat 'n aansienlike impak op 'n pasiënt se lewenskwaliteit het. In 'n studie wat deur Majumdar *et al.* (2003:2411) gedoen is, was die voorkoms van kroniese suurverwante siektes 2.3%. Die koste vir behandeling van suurverwante siektes maak 'n groot deel van voorgeskrewe medisyne uit (Whitaker, 1998:6). Die koste aan gesondheidsorg styg elke jaar. Dit lei tot 'n groter belangstelling in die ekonomiese evaluering van gesondheidsorg en mediese tegnologie (Anell & Svarvar, 2000:175). Verskaffers van gesondheidsorg neem nie meer besluite oor behandeling sonder om die koste daarvan te oorweeg nie. Die behandeling wat voorsien word, moet nie net van waarde wees nie, maar die waarde moet gedokumenteer wees om die besteding te regverdig. Ekonomiese evaluering poog om leiding aan beleidmakers, praktisyns, mediese fondse en instansies te gee wat moeilike besluite oor behandeling en gesondheidsdekking moet neem (Ellis *et al.*, 2002:271).

Die belangrikste doelwitte van hierdie studie was om die voorskryfpatrone en koste van teensuurmedisyne in 'n deel van die private gesondheidsorgsektor van Suid-Afrika, van 2001 tot 2006, te ondersoek met spesifieke verwysing na protonpompremmers en histamien-2-reseptor-antagoniste. 'n Longitudinale, retrospektiewe studie van die gebruik van teensuurmedisyne is gedoen op items wat deur 'n nasionale medisyne-eisedatabasis geëis is. Die vyf studiejare was 2001, 2002, 2004, 2005 en 2006. Al die studiejare het van 1 Januarie tot 31 Desember gestrek.

Dit is gevind dat die voorgeskrewe teensuurmedisyne van 2.74% van alle geëisde medisyne-items in 2001 na 2.50% in 2006 gedaal het. Dieselfde dalende neiging in die koste van teensuurmedisyne is waargeneem. Die koste het persentasiegewys van 4.89% (2001) na 3.72% (2006) afgeneem. Die gemiddelde koste per medisyne-item van die teensuurmedisyne

het egter van 2001 tot 2002 met 5.35% toegeneem (van R230.04 ± 176.29 tot R243.72 ± 184.18) en daarna van 2002 tot 2004 met 15.23% afgeneem. Van 2004 tot 2006 was daar weer 'n daling van 15.05% (R206.19 ± 179.42 tot R175.70 ± 172.55). Hierdie veranderinge in die gemiddelde koste van teensuurmedisyne was egter nie van praktiese betekenis nie.

In die studietydperk het protonpompremmers ongeveer die helfte van al die voorgeskrewe teensuurmiddels uitgemaak en meer as 70% van die totale koste van al die teensuuritems. Die gemiddelde koste van PPR's het van 2002 tot 2006 'n prakties betekenisvolle ($d > 0.8$) daling getoon (van R372.42 ± 156.62 tot R241.56 ± 77.21). H₂RA's het tussen 15.00% en 18.26% van alle teensuuritems bedra, terwyl dit tussen 9.68% en 16.85% van die totale koste van alle teensuurmedisyne beloop het.

Die aktiewe bestanddeel wat in 2001 en 2002 die meeste voorgeskryf was, was lansoprasool met esomeprasool die meeste in 2004 en omeprasool die meeste in 2005 en 2006. Lanzor® 30mg was van 2001 tot 2005 die teensuuritem met die hoogste totale koste, terwyl Pariet® 20mg dit in 2006 was. Zantac® 150mg bruistablette was tydens die vyf studiejare die H₂RA met die hoogste totale koste.

Die persentasie items van innoveerders het van 2001 tot 2002 met 4.50% afgeneem, van 2002 tot 2004 met 1.01% toegeneem en van 2004 tot 2006 weer met 31.06% afgeneem. Die klein toename in die persentasie innoveerderitems wat van 2002 tot 2004 geëis is, kan dalk deur die toetrede tot die mark van Nexiam® (esomeprasool) in 2002 verklaar word. Die totale bedrag wat vir generiese medisyne-items geëis is, het tussen 9.62% ($n = R1\ 788\ 242.25$ in 2001) en 30.75% ($n = R3\ 196\ 163.34$ in 2006) van die totale koste van die teensuuritems bedra.

Die gemiddelde daaglikse koste vir innoveerder medisyne-items was hoër as die gemiddelde daaglikse koste van generiese medisyne-items. Dit kan moontlik deur 'n laer gemiddelde koste vir generiese medisyne-items verklaar word.

Dit is ook gevind dat 'n regimen met twee middels tydens die vyf studiejare die meeste voorgeskryf is. Behandeling vir die uitwissing van *H. pylori*, wat 'n aantal antibiotikums ingesluit het, het van 2.72% in 2001 na 5.05% in 2006 toegeneem.

Die voorgeskrewe daaglikse dosis vir die meeste aktiewe bestanddele van H₂RA's en PPR's het tydens die studietydperk redelik stabiel gebly. Dit blyk egter dat die voorgeskrewe daaglikse dosis van die aktiewe bestanddele van die PPR's meer konstant as dié van die H₂RA's was. Die mediaan van die verskillende aktiewe bestanddele van die PPR's was relatief meer

Opsomming

konstant as dié van die H₂RA's. Die variasie in die mediaan (die aantal dae waarvoor die betrokke medisyne-items geëis is) kan moontlik die verskille in die voorgeskrewe daaglikse dosis van die aktiewe bestanddele van die PPR's en H₂RA's verklaar.

Dit word ook aanbeveel dat generiese vervanging sowel as die gebruik van H₂RA as voorgeskrewe teenoor selfmedikasie verder ondersoek moet word om die moontlike besparing in koste te verbeter.

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conference of the academy of pharmaceutical sciences
as well as the pharmaceutical managers conference of
North-West (September 2007)**

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CHAPTER 1:

INTRODUCTION AND PROBLEM STATEMENT

1.1 INTRODUCTION

The focus of this dissertation was on the usage of acid reducing medicine with reference to economical aspects, according to a medicine claims database in a section of the private health care sector.

1.2 PROBLEM STATEMENT

The term acid-related disorders include a variety of medical conditions. These disorders include: dyspepsia, gastroesophageal reflux disease (GORD), benign peptic ulcers of the stomach and duodenum, ulcers secondary to the use of conventional non-steroidal anti-inflammatory drugs (NSAIDs), and ulcers due to Zollinger-Ellison syndrome (Hoogerwerf & Pasricha, 2001:1005).

Gastrointestinal problems account for 8 to 10% of the workload of a general practitioner (GP) in the UK, and this figure is likely to apply to the workload of other primary care physicians in different parts of the world (Whitaker, 1998:5). It is estimated that about half of these consultations will be for patients with upper gastrointestinal symptoms, including dyspepsia and gastroesophageal reflux (Whitaker, 1998:5).

Forty percent of adults in the UK suffer from dyspepsia (Prescribing Pricing Authority, 2004). Only 5% consult their GP each year (Locke *et al.*, 1997:1455). Peptic ulcer disease (PUD) is present in 15 to 20% of patients with dyspepsia (Logan & Delaney, 2001:675).

Locke *et al.* (1997:1453) found that the symptoms of gastro-esophageal reflux were very common in a predominantly white population residing in Olmsted County, Minnesota. The prevalence of heartburn and acid regurgitation symptoms during a 12 months period were 42% and 45%. Frequent symptoms (at least weekly) of heartburn and/or regurgitation were reported by 20%. The majority reported that heartburn was of moderate severity and had a duration of 5 years or more (Locke *et al.*, 1997:1454).

In a population-based cohort study conducted among the members of a managed care organisation the prevalence of chronic acid-related disorders was 2.3%. The most common acid-related disorder in this study was gastroesophageal reflux disease, present in 59% of

patients. Presumptive dyspepsia was present in 35% of the patients. Of the 1458 patients with uninvestigated dyspepsia, almost two thirds were aged ≥ 50 years. Relatively few patients (6%) had a diagnosis of PUD. PUD patients were older, more likely to be male and more likely to be African American (Majumdar *et al.*, 2003:2411).

Gastro-oesophageal reflux disease (GORD) is a highly prevalent and chronic condition that has a considerable impact on the patient's quality of life and poses the risk of serious complications, such as Barrett's esophagus (Jasoni *et al.*, 1999:S18; Bytzer, 2003:S37; Holtmann *et al.*, 2004:1032).

It is estimated that by 2020, >16% of people in the United States will be ≥ 65 years of age and that nearly 20 million will be >85 years of age. Aging imparts a variety of physiologic changes in the oropharynx, esophagus and stomach that increase the risk for esophageal and gastrointestinal disorders. Older individuals also tend to have a higher prevalence of comorbid factors, such as *Helicobacter pylori* (*H.pylori*) infection, smoking, the presence of other diseases or the use of medications (e.g. NSAIDs), thus increasing their risk of acid-related disorders. Given these physiologic and comorbidity factors, the elderly are at higher risk for GORD, drug-induced oesophagitis, PUD and complications related to the use of NSAIDs (Greenwald, 2004:8S).

Upper gastrointestinal diseases represent not only a significant volume factor for the busy GP but also a major financial consideration with respect to the costs of drug prescribing and investigations (Whitaker, 1998:6). The management of acid-related disorders has been dramatically altered by the discovery of the development of proton pump inhibitors (PPIs). PPIs can currently be considered the most potent acid reducing medicine (Tutuian & Castell, 2003:51; Andersson & Carlsson, 2005:294). The use of PPI constitutes the largest expense for any single drug group in the United Kingdom (Hungin & Rubin, 1999:451).

According to a study conducted by Farmer (2001:208), who used a medicine claims database, Interpharm Data systems® in South Africa, the proton pump inhibitor cost for all the prescriptions issued was R17 426 608,51 in 46 646 cases representing 12.4% of the cost of all the prescriptions issued during the study period.

In a study conducted by Vincze *et al.* (2001:460) the *H.pylori* recurrence rate was very low (1.25%) during the 1-year period. The benefit of *H.pylori* eradication in peptic ulcer disease is clearly shown. It was found that over half of the ulcer patients had some symptoms 1 year after the successful eradication, and 36% of them were taking histamine-2 receptor antagonist (H_2RA) regularly. Only one third of the patients became symptom-free 1 year after the

successful eradication. This underlines the importance of follow-up of these patients after the eradication. Eradication therapy for acid-related diseases is generally more expensive, initially, than conventional therapies. The major benefit lies in the prevention of future relapses and complications and a reduction in the costs associated with these relapses (Byrne & Murray, 1999:237).

According to Ellis *et al.* (2002:271) our society is unwilling to pay for every aspect of medical care. Interest in economic evaluation of health care and medical technologies has increased substantially during the past decade (Anell & Svarvar, 2000:175). This is the result of the persistent escalation of health care expenditure. Health care providers no longer make treatment decisions independent of the consideration of the resultant cost. The treatment provided must not only provide value but the value must be documented to justify spending money. Economic evaluation research has emerged to offer guidance to policy makers, practitioners, health plans and institutions facing difficult treatment and coverage decisions (Ellis *et al.*, 2002:271).

From the foregoing discussion, it is imperative that research should be performed regarding the necessity of acid reducing medicine and the utilisation and the cost of implications associated with these drugs.

1.3 RESEARCH QUESTIONS

The following research questions can be formulated from the foregoing discussion:

- What gastrointestinal tract disorders are acid-related disorders?
- What do acid-related disorders entail?
- What does the management of acid-related disorders entail?
- What does managed health care entail?
- What do pharmaco-economics and drug utilisation entail, with special reference to acid reducing medicine?
- What has the prescribing patterns (prevalence) of acid reducing medicine been in South Africa, from 2001 to 2006?
- What has cost of acid reducing medicine been in South Africa, from 2001 to 2006?

- Which acid reducing medicine has been most commonly used in South Africa, from 2001 to 2006?
- What have the utilisation patterns of the different types (sub-pharmacological groups) of acid reducing medicine in South Africa been, from 2001 to 2006?
- How has generic substitution influenced the cost of acid reducing medicine and the choice regarding the usage of acid reducing medicine, from 2001 to 2006.
- Which recommendations can be formulated regarding the prescribing patterns of acid reducing medicine?

1.4 RESEARCH OBJECTIVES

This research project included general as well as specific objectives.

1.4.1 GENERAL OBJECTIVE

The general objective of this study was to review the prescribing patterns and cost of acid reducing medicine according to a medicine claims database for the period 2001 to 2006 in a section of South Africa's private health care market.

1.4.2 SPECIFIC OBJECTIVES

The specific objectives of the literature study included the following:

- To investigate acid-related disorders and their treatment.
- To conceptualise what managed health care, pharmaco-economics and drug utilisation entail, with special reference to acid reducing medicine.

The specific objectives of the empirical study included the following:

- To investigate the possible differences in the utilisation patterns and/or cost of medicine in general, before and after the implementation of the pricing regulations in May 2004.
- To investigate the prevalence and prescribing patterns of medicine items in general, as well as the costs associated with these medicine items.
- To investigate the prevalence and prescribing patterns of gastro-intestinal (GI) medicine items, as well as the costs associated with these medicine items.

- To analyse the prescription patterns of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.
- To analyse the prescribing patterns for different types (sub-pharmacological groups) of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.
- To determine the prevalence of acid reducing medicine items according to trade name and active ingredients.
- To analyse the prescribing patterns for individual acid reducing medicine items in South Africa, as well as the costs associated with these medicine items.
- To determine the influence of generic substitution on the cost and prescribing patterns of acid reducing medicine.
- To determine the prevalence and cost of combinations (PPIs prescribed together with amoxicillin, bismuth, clarithromycin, metronidazole and tetracycline on one prescription) used in the treatment of *H.pylori*.
- To determine the prescribed daily dose for acid reducing medicine with special reference to H₂RAs and PPIs according to active ingredient, strength and innovator or generic medicine item.

1.5 RESEARCH METHOD

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

1.5.1 PHASE ONE: LITERATURE REVIEW

The literature review was divided into two steps (refer to chapter 2). The first step was a discussion of acid-related disorders and the treatment thereof. In this discussion an overview was given of the definitions, etiology, clinical findings (signs and symptoms), pathogeneses and complications of the different acid-related disorders. The pharmacology overview, which included the mechanism of action, dosage, tolerability and drug interactions, of the different acid reducing medicine was also addressed.

In the second step, managed health care, pharmaco-economics and drug utilisation were defined and discussed with reference to the prescribing patterns of acid reducing medicine (refer to chapter 3).

1.5.2 PHASE TWO: EMPIRICAL INVESTIGATION

The empirical investigation consisted of the following:

- **Defining the research method**

A retrospective drug utilisation study was done on data provided by Interpharm Data systems®, a medicine claims database in the private health care sector, with the focus on the years, 2001 to 2006, in order to obtain the specific objectives for this study (refer to section 4.3).

- **The selection of the study population**

The total population consisted of all the prescriptions claimed through the medicine claims database during 2001, 2002, 2004, 2005 and 2006. The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for the whole 2003. Thus the prescribing patterns and costs of drugs associated with this period could not be compared with the other periods. In turn the study population consisted only of those prescriptions containing acid reducing medicine items during 2001, 2002, 2004, 2005 and 2006.

- **The selection of measuring instruments**

The following measuring instruments were identified and implemented in this study: prevalence (refer to section 4.6.1), frequency, cost (refer to section 3.4.4 and section 4.6.3), cost prevalence index and effect size (d-values) (refer to section 4.7.3.4). Statistical calculations namely arithmetic mean/average, percentage and standard deviation were used in this study (refer to section 4.7.3).

- **Data analysis**

The Statistical Analysis system (SAS for Windows, 9.1, 2006) was used to analyse the data.

- **Ethical aspects**

Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the medical scheme administrator providing the data to ensure confidentiality. Thus no specific patient, medical practice, pharmacy or medical scheme could be identified. The confidentiality of information was maintained throughout the study.

The data used in this study were analysed with permission from the Pharmacy Benefit Management (PBM) Company, utilising Interpharm Data systems (Pty.) Ltd. database.

- **The report and discussion of the results of the empirical investigation**

Data for the analysis were obtained from one medicine claims database, thus, limiting external validity, implying that results can only be generalised to the specific database used, as well as to the specific study population. The reports and discussions of the results of the empirical investigation were illustrated graphically or in tables to achieve the set claims of the empirical investigation. A detailed overview of the reports and discussions will follow in chapter 5 of this dissertation.

- **Conclusion, limitations and recommendations based on the results of the empirical investigation**

A conclusion based on the results of the literature survey and the empirical investigation, as well as the recommendations resulting from this study on the prescribing patterns of acid reducers will be described in chapter 6. The limitations experienced during this study will also be discussed in chapter 6.

1.6 CHAPTER DIVISION

The division of chapters will be as follow:

Chapter 1: Introduction and problem statement

Chapter 2: Acid-related disorders and the treatment thereof with acid reducing medicine: a brief overview

Chapter 3: An overview: pharmaco-economics and drug utilisation review

Chapter 4: Empirical investigation

Chapter 5: Results and discussion

Chapter 6: Conclusions, recommendations and limitations

1.7 SUMMARY

In this chapter an overview of the problem statement was presented. A few research questions were stated and the general and specific research objectives were formulated. The research method was briefly described as well as the division of chapters.

CHAPTER 2:

ACID-RELATED DISORDERS AND THE TREATMENT THEREOF WITH ACID REDUCING MEDICINE: A BRIEF OVERVIEW

2.1 INTRODUCTION

This chapter focuses on gastrointestinal (GI) system (with specific reference to the oesophagus and the stomach), the physiology of gastric secretion, acid-related disorders and acid reducing medicine. For the purpose of this study dyspepsia, peptic ulcer disease (PUD), gastro-oesophageal reflux disease (GORD) and Zollinger-Ellison syndrome are identified as acid-related disorders. This chapter provides a short overview on the effects of demographic and environmental factors on the prevalence estimates on the different acid-related disorders. The mechanism of action, therapeutic indication, adverse effects and drug interactions of acid reducing medicine will be discussed shortly.

2.2 GASTROINTESTINAL (GI) SYSTEM

The GI system consists of the alimentary canal and the digestive tract. It begins in the oral cavity of the mouth and ends at the anus. The major structures of the GI system include the oral cavity (mouth, tongue and pharynx), the oesophagus, the stomach, the small intestine (duodenum, jejunum and ileum), the large intestine (cecum, colon and rectum) and the anus. The accessory organs and glands that contribute to the digestive process are the salivary glands, the pancreas, the gallbladder and the liver. The main functions of the GI system are digestion of food particles and absorption of the digestive contents (nutrients, electrolytes, minerals and fluids) into the circulatory system for cellular use (Kee & Hayes, 2000:738).

2.2.1 OESOPHAGUS

The oesophagus is a muscular tube (approximately 25 cm long) with an average diameter of 2 cm that extends from the pharynx to the stomach (Moore & Dalley, 1999:221). The oesophagus has two sphincters: a superior oesophageal (hyperpharyngeal) sphincter and a lower oesophageal sphincter, which prevents gastric reflux into the oesophagus, a condition called reflux oesophagitis (Kee & Hayes, 2000:739).

2.2.2 STOMACH

The stomach is a hollow organ that lies between the oesophagus and small intestine (Moore & Dalley, 1999:226). It can hold 1000 to 2000 ml of gastric contents and empties in 2 to 6 hours depending on gastric content and motility. Two sphincters, the cardiac sphincter, which lies at

the upper opening of the stomach, and the pyloric sphincter, located at the lower portion of the stomach or the head of the duodenum, regulate the entrance of food to the stomach (Kee & Hayes, 2000:739).

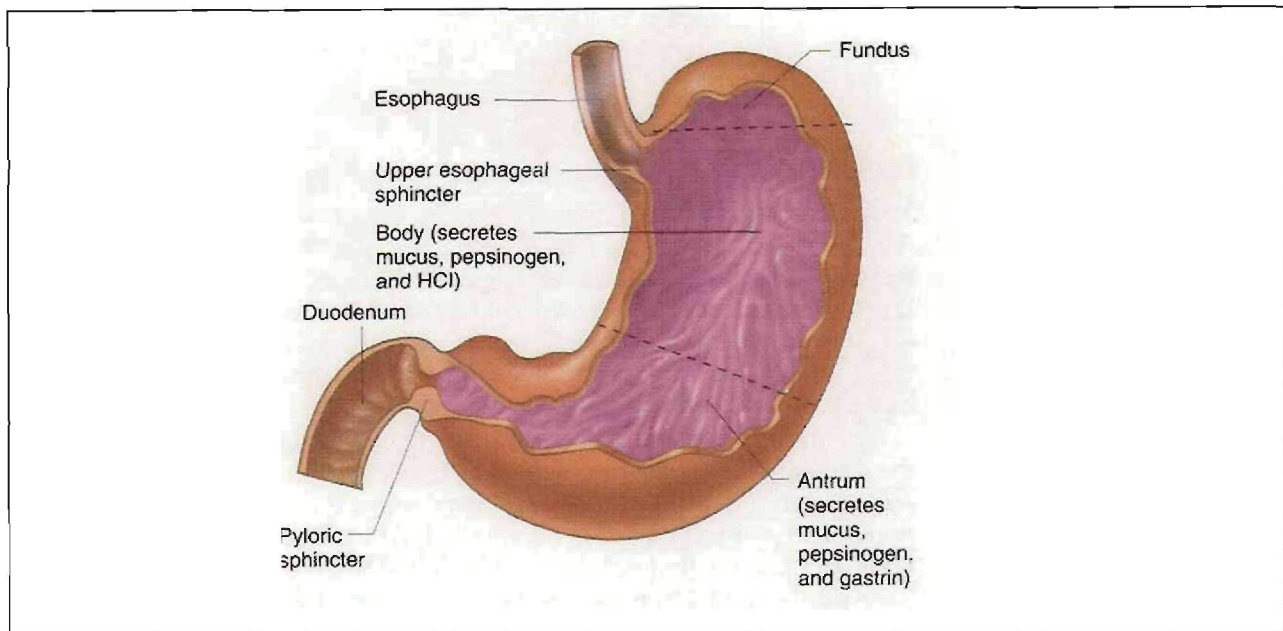


Figure 2.1: Abdominal part of the oesophagus, stomach and proximal part of the duodenum (Vander *et al.*, 2001:571).

The interior lining of the stomach has mucosal folds that contain glands (refer to figure 2.2 for an illustration of the gastric glands) that secrete gastric juices. The four cells in the stomach mucosa that secrete these juices are

- the chief cells, which secrete the enzyme precursor pepsinogen (pepsin);
- the parietal cells, which secrete hydrochloric acid (HCl);
- the gastrin-producing cells, which secrete gastrin, a hormone that regulates enzyme release during digestion; and
- mucus-producing cells that release mucus to protect the stomach lining (Kee & Hayes, 2000:739).

A different cell type secretes each of the three major exocrine secretions (mucus, acid and pepsinogen) of the stomach. Figure 2.1 illustrates the parts of the stomach responsible for these secretions. In addition, enterochromaffin-like (ECL) cells, which release the paracrine

agent histamine, and cells that secrete the peptide messenger somatostatin, are scattered throughout the tubular glands (Vander *et al.*, 2001:571).

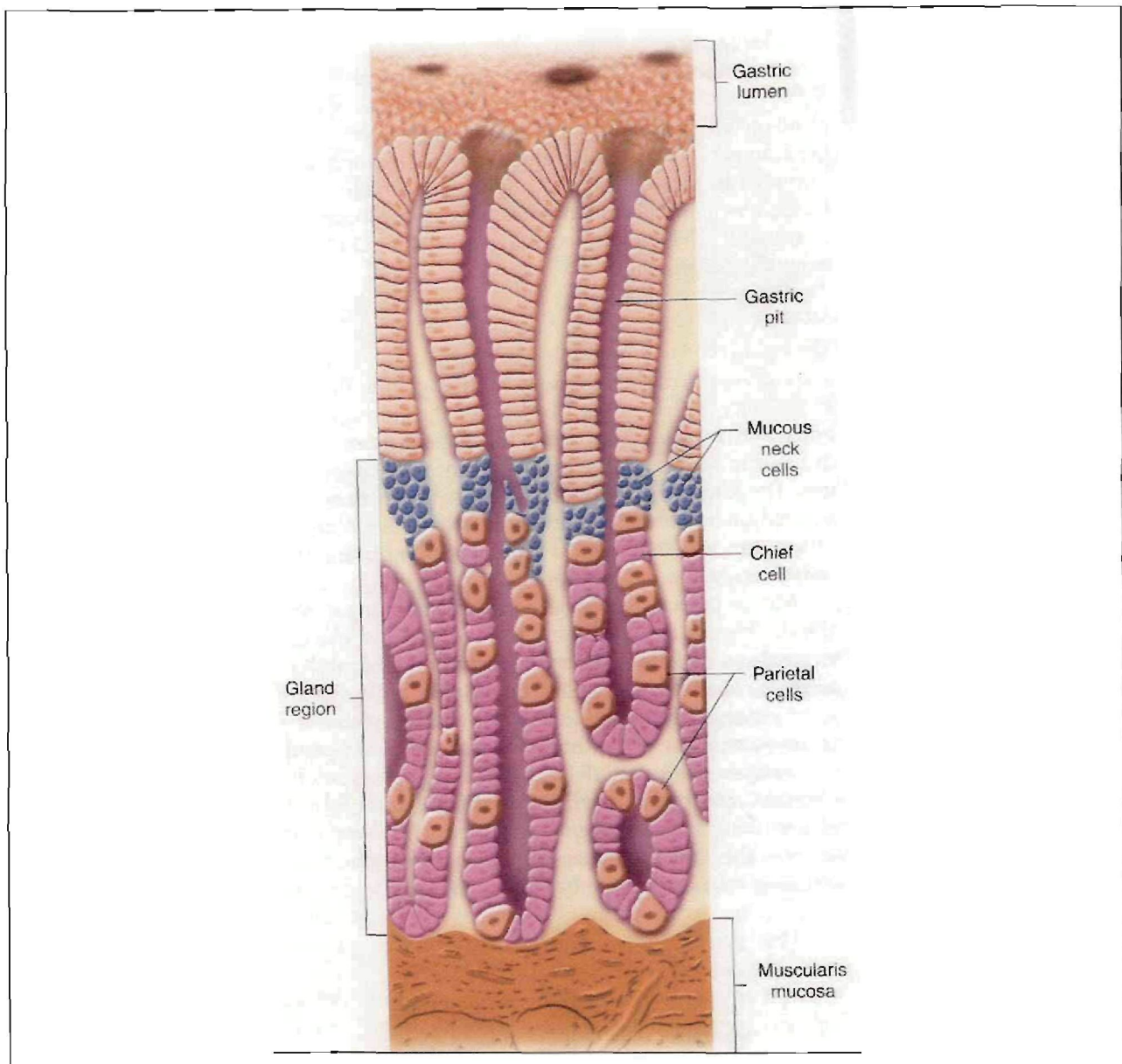


Figure 2.2: Gastric glands in the body of the stomach (Vander *et al.*, 2001:572).

2.3 PHYSIOLOGY OF GASTRIC SECRETION

Gastric acid secretion is a complex, continuous process controlled by multiple central (neural) and peripheral (endocrine and paracrine) factors (Hoogerwerf & Pasricha, 2001:1006). This process is illustrated by figure 2.3.

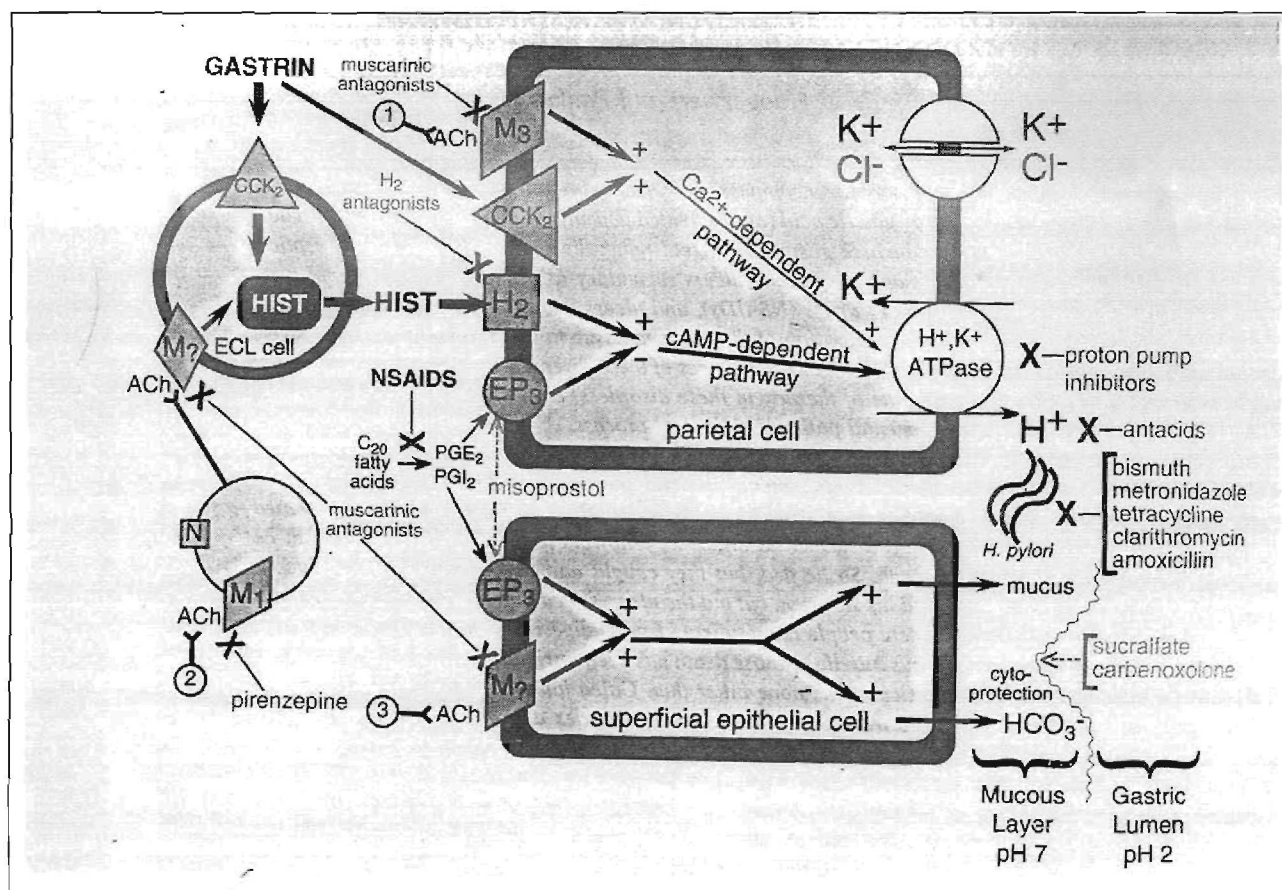


Figure 2.3: Physiological and pharmacological regulation of gastric secretions (Hoogerwerf & Pasricha, 2001:1006).

The most important structures in the central nervous system (CNS) involved in central stimulation of gastric acid secretion include: the dorsal motor nucleus of the vagal nerve (DMNV); the hypothalamus; and the nucleus tractus solitarius (NTS). Efferent fibres originating in the DMNV descend to the stomach via the vagus nerve and synapse with ganglion cells of the enteric nervous system (ENS). Acetylcholine (ACh) release from postganglionic vagal fibres can directly stimulate gastric acid secretion through a specific muscarinic cholinergic receptor subtype M_3 , located on the basolateral membrane of the parietal cells (see figure 2.2). The CNS probably modulates the activity of the ENS with ACh as its main regulatory neurotransmitter. The CNS generally is thought of as the main contributor to the initiation of gastric acid secretion in response to the sight, smell, taste, and anticipation of food ("cephalic phase"). ACh also indirectly affects the parietal cell through the stimulation of histamine release from the enterochromaffin-like (ECL) cells in the fundus (see figure 2.1) and the stimulation of gastrin release from the G cells in the gastric antrum (Hoogerwerf & Pasricha, 2001:1007).

Histamine is released from ECL cells through multifactorial pathways and is a critical regulator of acid production through the H_2 -receptor. ECL cells usually are found in close proximity to

parietal cells. Histamine activates the parietal cell in a paracrine fashion; it diffuses from its release site to the parietal cell (Hoogerwerf & Pasricha, 2001:1007).

Gastrin primarily is present in the antral G cells. Gastrin stimulates acid secretion predominantly in an indirect manner by causing the release of histamine from ECL cells (Hoogerwerf & Pasricha, 2001:1007).

Somatostatin, localised in the antral D cells, may inhibit gastrin secretion in a paracrine matter, but its role in the inhibition of gastric acid secretion remains to be defined (Hoogerwerf & Pasricha, 2001:1007).

Two major signalling pathways are present within the parietal cell: the cyclic AMP-dependent pathway and the Ca^{2+} -dependent pathway. Histamine uses the first pathway, while gastrin and Ach exert their effect via the second. The cyclic AMP-dependent pathway results in phosphorylation of parietal-cell effector proteins and the Ca^{2+} -dependent pathway leads to an increase in cytosolic Ca^{2+} . Both pathways activate the H^+ , K^+ -ATPase (the proton pump). The H^+ , K^+ -ATPase consists of a large α -subunit and a smaller β -subunit. This pump generates the largest ion gradient known in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8 (Hoogerwerf & Pasricha, 2001:1006).

Primary H^+ , K^+ -ATPase in the luminal membrane of the parietal cells pump hydrogen ions into the stomach's lumen. These primary active transporters also pump potassium into the cell, which then leaks back into the lumen through potassium channels. As hydrogen ions are secreted into the lumen, bicarbonate ions are being secreted on the opposite side of the cell into the blood, in exchange for chloride ions. This addition of bicarbonate lowers the acidity in the venous blood from the stomach (Vander *et al.*, 2001:572).

Increased acid secretion is the result of the transfer of H^+ , K^+ -ATPase proteins from the membranes of intracellular vesicles to the plasma membrane by fusion of these vesicles with the membrane, thus increasing the number of pump proteins in the plasma membrane (Vander *et al.*, 2001:572).

Vander *et al.* (2001:572) named four chemical messengers that regulate the insertion of H^+ , K^+ -ATPases into the plasma membrane and hence acid secretion: gastrin (a GI hormone), Ach (a neurotransmitter), histamine and somatostatin (two paracrine agents). Their respective specific receptors (M_3 , H_2 , CCK_2 receptors) have been anatomically and/or pharmacologically localised to the basolateral membrane of the parietal cell (Hoogerwerf & Pasricha, 2001:1006).

During a meal, the rate of acid secretion increases markedly as stimuli arising from the cephalic, gastric and intestinal phases alter the release of the four chemical messengers. During the

cephalic phase, increased activity of the parasympathetic nerves to the stomach's enteric nervous system results in the release of Ach from the plexus neurons, gastrin from the gastrin-releasing cells and histamine from ECL cells (Vander *et al.*, 2001:572).

Once food has reached the stomach, the gastric phase stimuli – distension by the volume of ingested material and the presence of peptides and amino acids released by digestion of luminal proteins – produce a further increase in acid secretion. These stimuli use some of the same neural pathways used during the cephalic phase, in that nerve endings in the mucosa of the stomach respond to these luminal stimuli and send action potentials to the enteric nervous system, which in turn, can relay signals to the gastrin-releasing cells. In addition, peptides and amino acids can act directly on the gastrin-releasing endocrine cells to promote gastrin secretion (Vander *et al.*, 2001:572).

The concentration of acid in the gastric lumen is itself an important determinant of the rate of acid secretion for the following reason. Hydrogen ions (acid) stimulate the release of somatostatin from endocrine cells in the gastric wall. Somatostatin then acts on the parietal cells to inhibit acid secretion; it also inhibits the release of gastrin and histamine. The net result is a negative-feedback control of acid secretion; as the acidity of the gastric lumen increases, it turns off the stimuli that are promoting acid secretions (Vander *et al.*, 2001:573).

Increasing the protein content of a meal increases acid secretion. This occurs for two reasons. First, the more protein ingested, the more peptides are generated in the stomach's lumen, and these peptides stimulate acid secretion. The second reason is more complicated and reflects the effects of protein on luminal acidity. Before food enters the stomach, the H^+ concentration in the lumen is high because there are few buffers present to bind any secreted hydrogen ions; therefore, the rate of acid secretion is low because high acidity inhibits acid secretion. The protein in food is an excellent buffer however, and so as protein enters the stomach the H^+ concentration drops as the hydrogen ions bind to the proteins. This decrease in acidity removes the inhibition of acid secretion. The more protein in a meal, the greater the buffering of acid and the more acid secreted (Vander *et al.*, 2001:573).

During the intestinal phase the stimuli in the early portion of the small intestine influence acid secretion by the stomach. High acidity in the duodenum triggers reflexes that inhibit gastric acid secretion. This inhibition is beneficial for the following reason: the digestive activity of enzymes and bile salts in the small intestine is strongly inhibited by acidic solutions and this reflex ensures that acid secretion by the stomach will be reduced whenever chyme entering the small intestine from the stomach contains so much acid that it cannot be rapidly neutralised by the bicarbonate-rich fluids simultaneously secreted into the intestine by the liver and pancreas (Vander *et al.*, 2001:574).

Acid, distension, hypertonic solutions and solutions containing amino acids and fatty acids in the small intestine reflexly inhibit gastric acid secretion. Thus, the extent to which acid secretion is inhibited during the intestinal phase varies; depending upon the volume and composition of the intestinal contents but the net result is the same – balancing the secretory activity of the stomach with the digestive and absorptive capacities of the small intestine (Vander *et al.*, 2001:574).

2.4 GASTRIC DEFENSE

The stomach protects itself from damage by gastric acid through several mechanisms such as the presence of intercellular tight junctions between the gastric epithelial cells, the presence of prostaglandins in the gastric mucosa, and secretion of bicarbonate ions into the mucin layer. Prostaglandins E₂ and I₂ inhibit gastric acid secretion by a direct effect on the parietal cell mediated by the EP₃ receptor. In addition, prostaglandins enhance mucosal blood flow and stimulate secretion of mucus and bicarbonate (Hoogerwerf & Pasricha, 2001:1007).

2.5 ACID-RELATED DISORDERS

The past 25 years have seen an improvement in the treatment and understanding of acid-related disorders. In particular, the introduction of selective H₂-receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) has made the medical control of acid secretion an effective means of therapy (Sachs *et al.*, 2002:835). The suppression of gastric acid secretion with acid reducing medicine has been the mainstay of medical treatment for patients with acid-related disorders. The principal pathological conditions in which it is useful to reduce acid secretion are dyspepsia, peptic ulceration (both duodenal and gastric), gastro-oesophageal reflux (GOR) and the Zollinger-Ellison syndrome.

2.5.1 DYSPEPSIA

2.5.1.1 DEFINITION

Dyspepsia is a symptom complex, rather than a specific disease entity and cannot be easily identified (Armstrong, 1996:38). Talley *et al.* (1999b:37) defined functional dyspepsia as a persistent or recurrent pain or discomfort centred in the upper abdomen. Centred implies that the pain or discomfort is mainly in or around the midline. Pain in the right or left hypochondrium is not considered to be representative of dyspepsia. The discomfort often described as indigestion, gaseousness, fullness or gnawing or burning pain localised in the upper abdomen or chest that has no specific cause on diagnostic evaluation (Beers & Berkow, 2004:236).

Table 2.1: Functional dyspepsia subgroups (Talley *et al.*, 1999b:39).

Subgroup	Definition
Ulcer-like dyspepsia	Pain centred in the upper abdomen is the predominant symptom.
Dysmotility-like dyspepsia	An unpleasant or troublesome non-painful sensation (discomfort) centred in the upper abdomen is the predominant symptom; this sensation may be characterised by - or associated with - upper abdominal fullness, early satiety, bloating or nausea.
Unspecified (non-specific) dyspepsia	Symptomatic patients whose symptoms do not fulfil the criteria for ulcer-like or dysmotility-like dyspepsia.

2.5.1.2 ETIOLOGY

According to Talley *et al.* (as quoted by Talley, *et al.*, 1999b:38) patients with dyspepsia can be subdivided into three main categories namely,

- those with an identified cause for the symptoms (e.g. chronic peptic ulcer disease, gastro-oesophageal reflux disease with or without oesophagitis, malignancy, pancreatic-biliary disease and medications);
- those with an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (e.g. *H.pylori* gastritis, histologic duodenitis, gallstones, visceral hypersensitivity, gastroduodenal dysmotility); and
- those with no identifiable explanation for the symptoms.

Those patients who have no definite structural or biochemical explanation for their symptoms are considered to have functional dyspepsia.

2.5.1.3 SIGNS AND SYMPTOMS

Discomfort may be characterised by – or associated with - upper abdominal fullness, early satiety, bloating or nausea (Talley *et al.*, 1999b:38). These symptoms are defined in table 2.2. Eating may worsen or relieve symptoms. Other associated symptoms may include anorexia

nervosa and nausea. Dysphoric states (e.g. anxiety and depression) may often occur, particularly among patients with more refractory symptoms (Beers & Berkow, 2004:237).

Table 2.2: The spectrum of dyspepsia symptoms and recommended definitions (Talley *et al.*, 1999b:38).

Symptom	Definition
Pain centred in the upper abdomen	Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain.
Discomfort centred in the upper abdomen	A subjective, unpleasant sensation or feeling that is not interpreted as pain according to the patient and which, if fully assessed, can include any of the symptoms below.
Early satiety	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished.
Fullness	Unpleasant sensations like the persistence of food in the stomach; this may or may not occur post-prandially (slow digestion.)
Bloating in the upper abdomen	Tightness located in the upper abdomen; it should be distinguished from visible abdominal distension.
Nausea	Queasiness or sick sensation; a feeling of the need to vomit.

2.5.1.4 DIAGNOSIS

Diagnosis can be made by a careful history, physical examination and an upper endoscopy during a symptomatic period of antisecretory therapy (Beers & Berkow, 2004:237). According to Talley *et al.* (1999b:38) patients need to have been investigated to rule out relevant organic disease. Functional dyspepsia therefore remains a diagnosis of exclusion. It is recommended that functional dyspepsia be defined as illustrated by Table 2.3.

Table 2.3: Diagnostic criteria for functional dyspepsia (Talley *et al.*, 1999b:38).

Symptoms follow a chronic course of at least 12 weeks, which need not be consecutive, within the preceding 12 months of

- persistent or recurrent dyspepsia (pain or discomfort centred in the upper abdomen); and
- no evidence of organic disease (including an upper endoscopy) that is likely to explain the symptoms; and
- no evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not irritable bowel).

2.5.1.5 TREATMENT

In most patients there is a clear link between clinical symptoms and food intake. Dyspeptic symptoms may be reduced by avoiding offending foods, high fat diet, coffee, alcohol and cigarette smoking. If early satiety, postprandial bloating or nausea is predominant, taking six small low fat meals per day may help decrease the intensity of the symptoms (Allescher, 2006:6). There is no evidence that life-style modifications would truly be efficacious (Talley *et al.*, 1999a:1144, Talley *et al.*, 1999b:38).

According to Talley *et al.* (1999a:1143) there are at least four major strategies for the management of dyspepsia. Firstly, there is a wait-and-see strategy of reassurance or over-the-counter (OTC) antacids or H₂RAs, with re-evaluation if this fails. Secondly, there is an empirical therapy strategy (e.g. prescribing an antisecretory or prokinetic agent), reserving endoscopy or other testing for those who are unresponsive or have an early symptomatic relapse. With the third approach management is based on symptom patterns or *H.pylori* status, with the goal of targeting further treatment and investigations more appropriately. The benefits of treatment of *H.pylori* in functional dyspepsia outweigh the risks. The final approach is to refer all patients with dyspepsia for prompt upper endoscopy (Beers & Berkow, 2004:237; Talley *et al.*, 1999a:1143). Each of these strategies has strengths and weaknesses that will be illustrated in table 2.4.

Table 2.4: Strategies for the management of uninvestigated dyspepsia (Talley *et al.*, 1999a:1137).

Strategy	Advantages	Disadvantages	Utility
OTC therapy e.g. antacid, H ₂ RA.	Cheap. Widely available.	Inadequate treatment of serious disease including peptic ulcer.	First onset of dyspepsia of short duration.
Empiric therapy e.g. antisecretory, prokinetic.	Can be tailored on symptom presentation. Cheap in those with none or few recurrences.	Does not provide as much reassurance as endoscopy. Inappropriate treatment of ulcer disease.	<i>H.pylori</i> – negative young dyspeptics.
High-dose PPI (reflux test).	May help to identify GORD.	Placebo response may mislead. Inappropriate treatment of ulcer disease.	<i>H.pylori</i> – negative young dyspeptics if reflux is a possibility.
<i>H.pylori</i> testing and endoscopy.	Fewer endoscopies. Allows earlier diagnosis of gastric cancer.	Expensive. May increase the endoscopy workload.	Regions where gastric cancer incidence is high and endoscopy is affordable.
<i>H.pylori</i> testing and treatment.	Cheaper than endoscopy. Provides reassurance.	May not provide as much reassurance for patients worried about malignancies.	Young patients without alarm features in regions where gastric cancer is rare.

Table 2.4 (Continued): Strategies for the management of uninvestigated dyspepsia (Talley *et al.*, 1999a:1137).

Strategy	Advantages	Disadvantages	Utility
Empiric <i>H.pylori</i> therapy without prior testing.	Cheap option initially.	Over treat the patient population.	Regions where <i>H.pylori</i> is highly prevalent and referral for endoscopy or testing is not an option.
Endoscopy.	Provides reassurance to both patient and doctor.	Expensive.	Patients with alarm features. Non-responders to initial medical therapy.

Antacids are often used by patients as OTC medicine prior to visiting a doctor (Allescher, 2006:6).

In patients with new onset dyspepsia or patients with dyspepsia first consulting their doctor, it is worthwhile to subdivide patients into groups with and without alarm features. Alarm features include an age threshold (randomly set at age 50 years in Western countries but varying depending on the country-specific incidence of gastric cancer), specific signs and symptoms (e.g. fever > 38.5°C, night sweat, weakness, weight loss > 3 kg, recurrent vomiting, progressive dysphagia, odynophagia, bleeding, severe localised pain, anaemia, jaundice, an abdominal mass, lymphadenopathy, a family history of upper gastrointestinal cancer or previous gastric surgery) and chronic NSAID use which cannot be ceased (Allescher, 2006:5; Talley *et al.*, 1999a:1142).

Patients presenting with alarm features should undergo prompt endoscopy whenever possible (Allescher, 2006: 5; Talley *et al.*, 1999a:1142).

In dyspepsia without alarm features, patients who have had symptoms for less than 4 weeks, can be managed initially with OTC medications such as antacids or low-dose H₂RA (Talley *et al.*, 1999a:1144).

In patients who present with symptoms for 4 weeks or longer or a history of recurrent symptoms that do not require prompt endoscopy, more specific approaches are indicated. In general

H.pylori testing and treatment is recommended as the next step (refer to section 2.5.2.6 regarding *H.pylori* eradication). The urea breath test (UBT) is preferred to test the patient's *H.pylori* status (Talley *et al.*, 1999a:1144).

In *H.pylori* – negative patients with 4 weeks or more of dyspepsia, the likely clinical diagnosis is functional dyspepsia. Atypical GORD also needs to be considered. Treatment options for *H.pylori* – negative patients are either a PPI test for reflux (e.g. double dose PPI for 2 weeks) or empirical therapy with standard doses of an antisecretory or a prokinetic agent for 1 month (Talley *et al.*, 1999a:1144).

The use of omeprazole as a diagnostic tool for GORD is supported by Bate *et al.* (1999:65). The PPI test for reflux (omeprazole test) seems to be a sensitive, cost effective diagnostic tool for detecting GORD as the cause of heartburn. This strategy results in cost savings and decreased use of invasive diagnostic tests. The cost savings result from the 64% reduction in the number of upper endoscopies performed and a 53% reduction in the use of oesophageal pH monitoring (Fass *et al.*, 1999:2165).

Patients with ulcer-like dyspepsia (see table 2.1) are more likely to benefit from potent antisecretory therapy than patients with dysmotility-like (see table 2.1) dyspepsia (Talley *et al.*, 1999a:1144). The vast majority of patients presenting with dyspepsia are likely to benefit from a course of PPI (Peura, 2001:S65). If the treatment is successful it should be stopped after 4 weeks (Talley *et al.*, 1999a:1144).

Therapy can be reinstituted for short periods if symptoms relapse. If the patient fails to respond after 4 weeks of standard empirical therapy, switching to an alternative drug class (e.g. from a prokinetic to an antisecretory) for up to 4 weeks is the next reasonable step. If this fails and patients have not yet undergone endoscopy, this can be considered but is not essential (Talley *et al.*, 1999a:1144).

Talley *et al.* (1999a:1145) found it more cost effective to test and treat *H.pylori* infections first rather than applying other management approaches. According to Delaney *et al.*, (2000:1968) initial endoscopy in patients over age 50 might be a cost effective intervention. In contrast Rabeneck *et al.* (2002:3049) concluded in their double blind, randomised, placebo-controlled trial that an initial 6 week course of either placebo or omeprazole reduces the need for endoscopy over a 1 year follow up.

Results from a probabilistic sensitivity analysis conducted by Goeree *et al.* (2002:322) showed that the best way of managing patients with dyspepsia depends on the maximum amount the

society is willing to pay to achieve health improvement. The optimal management strategy is to prescribe a PPI to relieve symptoms followed by a H₂RA to prevent symptomatic recurrence.

In a cost-utility analysis of the management strategies of dyspepsia it was projected that empirical treatment with a PPI was to provide the greatest quality-adjusted survival. Empirical treatment with H₂RA was anticipated to be the least costly of the alternatives. This study concluded that the choice between a PPI and H₂RA depends on the impact of dyspepsia on quality of life (Heudebert *et al.*, 2000:178).

Talley *et al.* (1999a:1142) recommends the strategy illustrated by figure 2.4 for the management of uninvestigated dyspepsia.

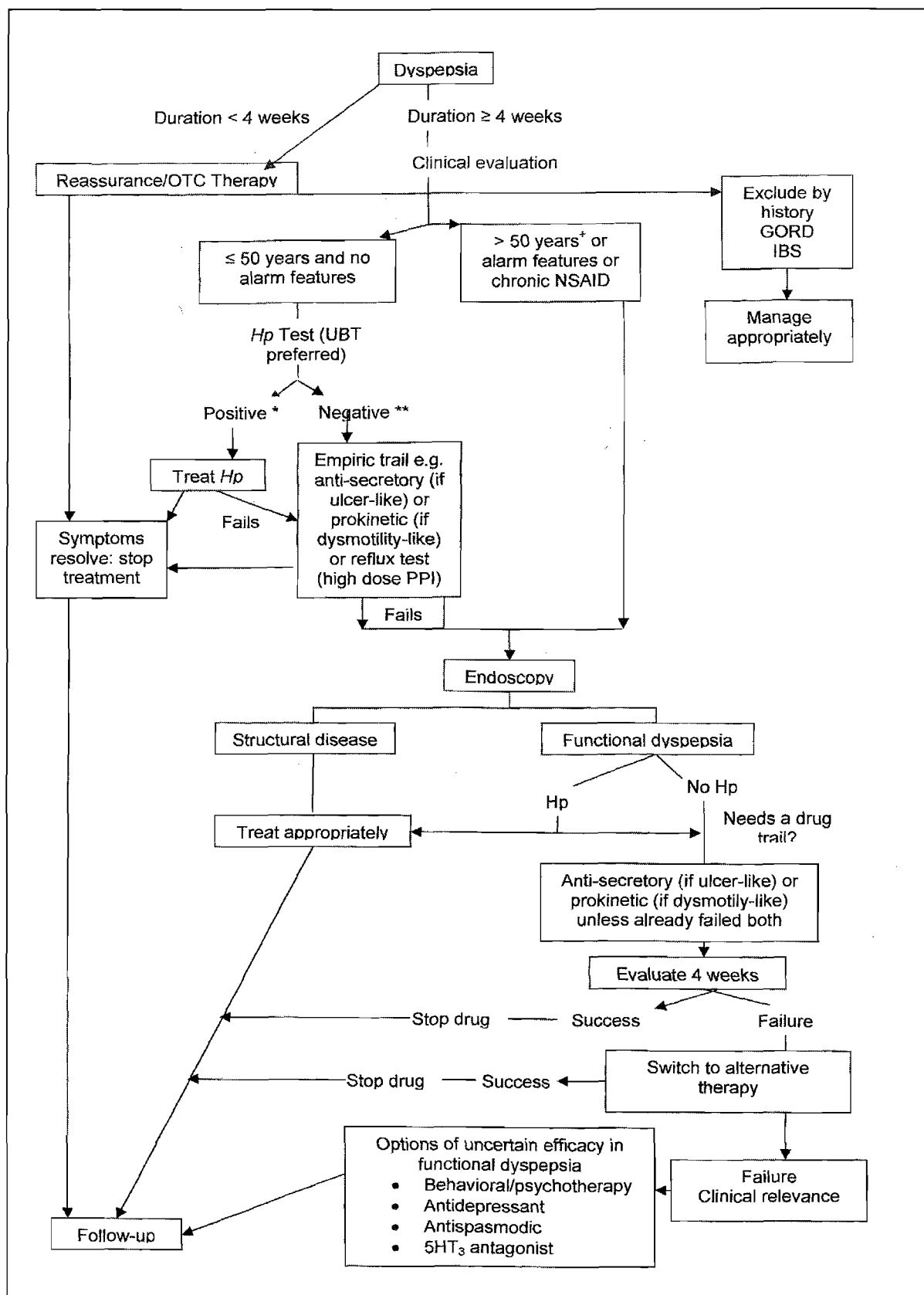


Figure 2.4: Management of dyspepsia in western nations (Talley *et al.*, 1999a:1143).

2.5.2 PEPTIC ULCER DISEASE (PUD)

2.5.2.1 DEFINITION

Peptic ulcer is a term used to describe a group of ulcerative disorders that occur in areas of the GI that are exposed to acid-pepsin secretions. Thus a peptic ulcer is an excoriated segment of the GI mucosa, typically in the stomach (gastric ulcer) or first few centimeters of the duodenum (duodenal ulcer), which penetrates through the muscularis mucosa (Beers & Berkow, 2004:250). PUD with its remissions and exacerbations represents a chronic health problem.

2.5.2.2 ETIOLOGY

According to Dipiro (2003a:268) the three common forms of peptic ulcers include

- *H.pylori* – associated ulcers
- NSAIDs – induced ulcers
- Stress-related mucosal damage

2.5.2.3 SIGNS AND SYMPTOMS

Most patients have few or even no symptoms. Symptoms depend on the location of the ulcer (see Table 2.5) and the patient's age. Pain is the most common symptom; it is often localised in the epigastrium and relieved by food or antacids. The pain is described as burning, gnawing or hunger but can present as vague discomfort, abdominal fullness or cramping (Dipiro, 2003a:268; Beers & Berkow, 2004:251). Patients with PUD often present with other dyspeptic symptoms such as heartburn, belching and bloating (Dipiro, 2003a:269).

Table 2.5: The comparison of symptoms of gastric and duodenal ulcers (Sands, 1999:1285; Dipiro, 2003a:268; Beers & Berkow, 2004:251).

Gastric ulcer	Duodenal ulcer
• Pains do not follow a consistent pattern (e.g. eating sometimes exacerbates rather than relieves pain): ➤ Pain is dull epigastric location near midline. ➤ Pain is early satiety. ➤ Pain is usually not relieved by food or antacid. • Nausea, vomiting, anorexia nervosa and weight loss more common with gastric ulcers.	• Pains tend to be consistent: ➤ Pains are absent when the patient awakens but appears in midmorning. ➤ Pain is episodic in nature lasting 30 minutes to 2 hours. ➤ Pain is relieved by food but recurs 2 to 3 hours after a meal. • Pain that awakens a patient at night, between 12 am and 3 am.

2.5.2.4 DIAGNOSIS

Diagnosis of peptic ulcer is suggested largely by history and is confirmed by the following studies: endoscopies, x-rays, cytology and multiple biopsies (Beers & Berkow, 2004:251).

2.5.2.5 COMPLICATIONS

Complications of ulcers caused by *H.pylori* and NSAIDs include: upper GI bleeding, perforation into the peritoneal cavity, penetration into an adjacent structure (e.g. pancreas, biliary tract or liver) and gastric outlet obstruction (Dipiro, 2003a:269).

2.5.2.6 TREATMENT

Patients with PUD should eliminate or reduce psychological stress, cigarette smoking and the use of NSAIDs (including aspirin). If the NSAID cannot be discontinued, consideration should be given to lowering the dose or changing to acetaminophen (paracetamol), a non-acetylated salicylate (e.g. salsalate), a relatively selective COX-2 inhibitor (nabumetone, etodolac), or a highly selective COX-2 inhibitor (e.g. celecoxib, rofecoxib). Co-administration with food, an H₂RA or PPI may decrease symptoms and mucosal damage (Dipiro, 2003a:270). Salas *et al.*, (2002) suggest in their study that the first-line drug therapy for patients diagnosed with gastric

ulcer should be a PPI, in preference to H₂RA. This study indicated that compared with ranitidine the PPIs provide faster onset of action, greater relief of symptoms and increased healing rates. According to Vakil and Fennerty (2003:566) peptic ulcer healing is similar when using standard doses of any PPI. Pantoprazole seems to provide a more favourable pharmaco-economic profile than omeprazole for the treatment of peptic ulcer and GORD (Van Hout *et al.*, 2003:643).

Patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms such as spicy foods, caffeine and alcohol (Dipiro, 2003a:270).

The issues to be considered when selecting a regimen for treatment of *H.pylori* infection include: cost, simplicity, effectiveness, side effects, rate of antibiotic resistance in the community, dose, duration, daily number of administrations and administration of the drugs with meals versus fasting (Dore *et al.*, 2002:859).

Treatment for *H.pylori* should be initiated with a PPI-based three-drug regimen (see Table 2.6), as they are most efficient, better tolerated and simpler. PPI-based three-drug regimen is also associated with better adherence (Dipiro, 2003a:270). According to Sung *et al.* (1999:1083) the MACH 1 study has earned great popularity for the PPI triple therapy as the first-line treatment for *H.pylori* infection. The MACH study compared different combinations of omeprazole and two antimicrobials. A 14-day course is preferred (Dipiro, 2003a:270). Two-drug regimens (see Table 2.6) are less effective than three-drug regimens and the inclusion of only one antibiotic may lead to anti-microbial resistance. Bismuth-based four-drug regimens (see Table 2.6) are effective but involve complicated dosing schedules and are associated with a higher incidence of adverse effects (Dipiro, 2003a:270).

Table 2.6: Suggested drug regimens used to eradicate *Helicobacter pylori* (Dipiro, 2003a:272).

Two-drug regimens	Three-drug regimens	Bismuth-based four-drug regimens
1. Clarithromycin, 500 mg tds x 14 days; 2. PPI ¹ , qid or bd x 14 to 28 days.	1. Clarithromycin, 500 mg bd; 2. Amoxicillin, 1 g bd or tds; 3. PPI ¹ , bd. 1, 2 & 3 → 10 to 14 days	1. BSS, 500 mg qid; 2. Metronidazole, 250 to 500 mg qid; 3. Tetracycline, 500 mg qid; 4. H ₂ RA or PPI ² mdu. 1, 2 & 3 → 14 days
1. Clarithromycin, 500 mg tds x 14 days; 2. RBC, 400 mg bd x 14 to 28 days.	1. Clarithromycin, 500 mg bd; 2. Metronidazole, 500 mg bd; 3. PPI ¹ , bd. 1, 2 & 3 → 10 to 14 days	1. BSS, 500 mg qid; 2. Metronidazole, 250 to 500 mg qid; 3. Clarithromycin, 250 to 500 mg qid; 4. H ₂ RA or PPI ² mdu. 1, 2 & 3 → 14 days
1. Amoxicillin, 1 g bd to tds x 14 days; 2. PPI ¹ , bd to tds x 14 to 28 days.	1. Amoxicillin, 500 mg bd; 2. Metronidazole, 500 mg bd; 3. PPI ¹ , bd. 1, 2 & 3 → 10 to 14 days	1. BSS, 500 mg qid; 2. Metronidazole, 250 to 500 mg qid; 3. Amoxicillin, 500 mg; 4. H ₂ RA or PPI ² mdu. 1, 2 & 3 → 14 days

Table 2.6 (Continued): Suggested drug regimens used to eradicate *Helicobacter pylori* (Dipiro, 2003a:272).

Two-drug regimens	Three-drug regimens	Bismuth-based four-drug regimens
	1. Clarithromycin, 500 mg bd; 2. Amoxicillin, 1 g bd; 3. RBC, 400 mg bd. 1, 2 & 3 → 14 days	
	1. Clarithromycin, 500 mg bd; 2. Metronidazole, 500 mg bd; 3. RBC, 400 mg bd. 1, 2 & 3 → 14 days	
	1. Clarithromycin, 500 mg; 2. Tetracycline, 500 mg; 3. RBC, 400 mg. 1, 2 & 3 → 14 days	

tds = Three times a day; qid = Four times a day; bd = Twice daily; RBC = Ranitidine bismuth citrate; BSS = bismuth subsalicylate; mdu = as directed using standard dosages.

¹ Use either omeprazole 20mg, esomeprazole 20mg, lansoprazole 30mg, rabeprazole 20mg, or pantoprazole 40mg bd; alternatively the total PPI daily dosage (e.g. omeprazole 40mg) may be given qid; only lansoprazole 30mg is indicated tds.

² In the setting of an active ulcer, acid suppression is added to hasten pain relief. When using an H₂RA (cimetidine, ranitidine, famotidine or nizatidine) may be used in ulcer-healing dosages (Table 2.7) for duration of 4 to 6 weeks; when using a PPI (omeprazole, esomeprazole, lansoprazole, rabeprazole or pantoprazole) may be used in ulcer-healing dosages (Table 2.7) for duration of 2 to 4 weeks.

Table 2.7: Oral drug regimens used to heal peptic ulcers or to maintain ulcer healing (Dipiro, 2003a:273).

Drug	Duodenal or gastric ulcer healing (mg/dose)	Maintenance of duodenal or gastric ulcer healing (mg/dose)
H₂RAs:		
• Cimetidine	300 qid, 400 bd, 800 hours	400 to 800 hours
• Famotidine	20 bd, 40 hours	20 to 40 hours
• Nizatidine	150 bd, 300 hours	150 to 300 hours
• Ranitidine	150 bd, 300 hours	150 to 300 hours
PPIs:		
• Omeprazole	20 to 40 daily	20 to 40 daily
• Lansoprazole	15 to 30 daily	15 to 30 daily
• Rabeprazole	20 daily	20 daily
• Pantoprazole	40 daily	40 daily
• Esomeprazole	20 to 40 daily	20 to 40 daily
Cytoprotective agent:		
• Sucralfate (g/dose)	1 qid, 2 bd	1 to 2 bd, 1 qid

qid = Four times a day; bd = Twice daily.

According to Howden and Hunt (1998:2335) the highest eradication rates are achieved with the following regimens:

- A PPI, clarithromycin and either amoxicillin or metronidazole for 2 weeks;
- Ranitidine bismuth citrate (RBC), clarithromycin and either amoxicillin, metronidazole or tetracycline for 2 weeks;

- A PPI, bismuth, metronidazole and tetracycline for 1 to 2 weeks.

In a single blind, prospectively randomised, parallel group, comparative, multicentre study which compared four treatment regimens lasting seven days of a PPI and two antibiotics in the eradication of *H.pylori*, it was concluded that all four treatment regimens were safe and efficacious in the eradication of *H.pylori* in patients with duodenal ulcer or non-ulcer gastritis, or both (Misiewicz *et al.*, 1997:739). The four treatment regimens were: LAC, LAM, LCM and OAM, where L is 30mg lansoprazole twice daily, A is 1 g of amoxicillin twice daily, M is 400mg of metronidazole twice daily, C is 250mg of clarithromycin twice daily and O is 20mg of omeprazole twice daily. In the presence of pretreatment metronidazole sensitive strains of *H.pylori* the treatments were of similar efficacy. In areas of high prevalence of metronidazole resistant strains of *H.pylori*, however, a regimen based on a PPI with amoxicillin and clarithromycin could be considered as first-line treatment (Misiewicz *et al.*, 1997:739).

In another multicentre, open, randomised trial conducted by Frevel *et al.* (2000:1156) it was concluded that both 7-day triple therapy combinations with either pantoprazole 40mg twice daily, clarithromycin 500mg twice daily and metronidazole 500mg twice daily or pantoprazole 40mg twice daily, amoxicillin 1000mg twice daily and clarithromycin 500mg twice daily were well-tolerated and highly effective in the eradication of *H.pylori* in patients with duodenal ulcer.

RBC in combination with clarithromycin and amoxicillin is comparable to PPIs using the same antibiotic combinations. It is recommended as an alternative regimen for the treatment of *H.pylori* infection and its related duodenal ulcers (Sung *et al.*, 1998:730). A study conducted by Spadaccini *et al.* (1998:997) confirmed that short-term triple therapy with either lansoprazole or RBC is equally effective and well tolerated.

The RBC-MACH conducted by Sung *et al.* (1999:1083) is a single-centre, open label, randomised trial. In this study dyspeptic patients with *H.pylori* infections were prospectively randomised to receive one of the following regimens: RBC 400mg, amoxicillin 1g, clarithromycin 500mg [RAC]; RBC 400mg, metronidazole 400mg, clarithromycin 500mg [RMC]; RBC 400mg, metronidazole 400mg, tetracycline 1g [RMT] (all given twice daily for 1 week) or RBC 400mg plus clarithromycin 500mg twice daily for 2 weeks [RC-2]. Both RAC and RMC achieved an all-patient-treated cure rate of over 90%. The RMT regimen showed consistently lower efficacy. The 2 week dual therapy regimen of RBC and clarithromycin showed no advantage over the RAC and RMC and was associated with a slightly higher rate of intolerance and drug violation as a result of the longer duration of therapy. Overall, the four regimens tested in this study were well tolerated with satisfactory patient compliance. Sung *et al.* (1999:1084) concluded that clarithromycin contributed greatly to the success of the RBC-

clarithromycin combination therapies and that the RBC-based triple therapies containing clarithromycin offer a simple, effective and safe choice for the treatment of *H.pylori* infections.

In a prospective, single centre study of consecutive dyspeptic *H.pylori* – infected patients it was suggested that this combination (omeprazole 20mg, tetracycline 500mg, metronidazole 500mg and bismuth sub citrate 240mg) of twice-a-day quadruple therapy should be considered as the first-line treatment for the eradication of *H.pylori* infections (Dore *et al.*, 2002:860). This regimen proved to be highly effective, both as initial therapy (99% eradication rate) and as rescue or salvage (98% eradication rate). The regimen was well tolerated since moderate or severe side effects were experienced by only 5% of patients.

Iacopini *et al.* (2005:573) conducted the first study in which levofloxacin and azithromycin were used together in a once-daily regimen. In their population, the once-daily triple therapy appeared as effective as a twice-daily triple therapy and associated with a less than half rate of poor compliance and with a significantly higher tolerability, in the absence of severe side effects.

Maintenance therapy with a low-dose H₂RA, PPI or sucralfate should be limited to high-risk patients who fail *H.pylori* eradication, patients with severe complications and those with *H.pylori* negative ulcers. Ulcers refractory to standard PPI doses (omeprazole 20mg/day) and standard or high-dose H₂RAs can usually be healed with higher PPI doses (omeprazole 40mg/day). Maintenance therapy with the PPI healing dose is often necessary to prevent recurrence. Most uncomplicated NSAID-induced ulcers heal with standard regimens of an H₂RA, PPI or sucralfate if the NSAID is discontinued. If the NSAID must be continued, PPIs are the drugs of choice because potent acid suppression is required to accelerate ulcer healing. If *H.pylori* are present, treatment should be initiated with an eradication regiment that contains a PPI. Patients at risk of developing serious ulcer-related complications while on NSAIDs should receive prophylactic co-therapy with misoprostol or a PPI. Patients with complicated ulcers (upper GI bleeding, obstruction, perforation or penetration) often require endoscopic or surgical treatment (Dipiro, 2003a:271).

According to Leontiadis *et al.* (2005) PPI treatment does not reduce mortality after ulcer bleeding, though it does reduce rates of rebleeding and, in general, the need for surgical intervention. This may be associated with important cost savings.

The eradication of *H.pylori* in North American patients with duodenal ulcer disease significantly decreased the chance of recurrent ulcers in the 6 months after completion of therapy (Laine *et al.*, 1998:1413). In a study conducted by Vincze *et al.*, (2001:460) the *H.pylori* recurrence rate was very low (1.25 %) during the 1-year period. Gisbert *et al.*, (2004:626) concluded in their

meta-analysis that *H.pylori* eradication therapy is more effective than antisecretory non-eradication therapy (with or without long-term maintenance antisecretory treatment) in the prevention of recurrent bleeding from peptic ulcer. In addition to efficacy, other relevant advantages of *H.pylori* eradication treatment - such as better compliance, better convenience and lower cost - favour the use of antibiotic therapy. All patients with peptic ulcer bleeding should be tested for *H.pylori* infection and eradication therapy should be prescribed to *H.pylori* - positive patients.

The treatment guidelines for PUD at Tygerberg Academic Hospital consist of a one week therapy with double dose PPI (e.g. pantoprazole 40mg twice daily) and 2 antibiotics (e.g. Amoxil[®], Klacid[®] or Flagyl[®]) if it is *H.pylori* related (Van Rensburg, 2006).

2.5.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

2.5.3.1 DEFINITION

According to Dipiro (2003b:216) GOR or reflux oesophagitis refers to the retrograde movement of gastric contents from the stomach into the oesophagus. GORD refers to any symptomatic clinical condition or histologic alterations that result from episodes of GOR. Thus GORD is the chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus (DeVault & Castel, 1999:1434).

2.5.3.2 ETIOLOGY

The presence of GORD indicates incompetence of the lower oesophageal sphincter. Factors that contribute to the competence of the gastro-oesophageal junction include: intrinsic sphincter pressure, the angle of the cardio-oesophageal junction, the action of the diaphragm, and gravity (when the patient is upright). GORD may lead to oesophagitis. Factors that contribute to the development of oesophagitis include: the caustic nature of refluxate, the inability to clear the refluxate from the oesophagus, the volume of gastric contents, and local mucosal protection functions (Beers & Berkow, 2004:232).

2.5.3.3 PATHOPHYSIOLOGY

Although the signs and symptoms of GORD are related predominantly to the effects of acid and pepsin, GORD is generally considered to be a manifestation of a motility disorder. Pathological GOR occurs as a result of impairment of the anti-reflux mechanism that comprises the lower oesophageal sphincter (LES) and crural diaphragm. Provided there is no structural lesion, such as a hiatus hernia, most reflux episodes are caused by inappropriate transient LES relaxations (TLESRs) that are triggered, often post-prandially, by gastric fundic distension. Gastrointestinal

dysmotility (causing delayed gastric emptying or impaired fundic relaxation), diet, and obesity all play a role, as might other factors such as estrogen (e.g. during pregnancy) and medications. GOR can also occur if baseline LES tone is reduced and more commonly, if there is a hiatus hernia. A hiatus hernia causes physical separation of the LES and the diaphragmatic crura such that they are unable to act in concert; as a result, gastric contents reflux more readily into the hernia, they are cleared less effectively into the stomach, and they are then more likely to reflux into the oesophagus, particularly in the recumbent position (Armstrong, 2005:589).

2.5.3.4 SIGNS AND SYMPTOMS

The most prominent symptom is heartburn, with or without regurgitation of gastric contents into the mouth (Beers & Berkow, 2004:232). Heartburn is described as a substernal sensation of warmth or burning that may radiate to the neck. It is waxing and waning in character and is often aggravated by activities that worsen GOR (e.g. supine position, bending over, eating a high-fat meal). Other symptoms include water brash (hypersalivation), belching and regurgitation. Atypical symptoms include non-allergic asthma, chronic cough, hoarseness, pharyngitis and chest pain that mimics angina (Dipiro, 2003b:217). Warning symptoms suggestive of complicated GORD include: dysphagia, bleeding, weight loss, choking (acid causing coughing, shortness of breath or hoarseness) and chest pain (DeVault & Castell, 1999:1435).

2.5.3.5 DIAGNOSIS

According to Dent *et al.* (2001:344) the key to diagnosis of GORD is the careful analysis of symptoms and history. Heartburn and regurgitation are both considered being specific symptoms for the diagnosis of GORD (Locke *et al.*, 1997:1450). Diagnosis based on symptoms can be aided by a trial of treatment (Dent *et al.*, 2001:344). Other methods for the accurate diagnosis of GORD incorporate: x-rays, oesophagoscopy, oesophageal manometry, pH monitoring, the Bernstein acid perfusion test and oesophageal biopsy (Beers & Berkow, 2004:232).

2.5.3.6 COMPLICATIONS

Inadequately treated GORD may lead to complications from long-term acid exposure such as continual pain, dysphagia and odynophagia (Dipiro, 2003b:217). Other severe complications of GORD include: oesophagitis, oesophageal stricture, hemorrhage, oesophageal ulcer and Barrett's metaplasia and oesophageal adenocarcinoma (Dipiro, 2003b:217; Beers & Berkow, 2004:232).

2.5.3.7 TREATMENT

Medical therapies for GORD include neutralising gastric acidity, decreasing gastric acid production, facilitating gastric emptying, improving oesophageal peristalsis and lower oesophageal sphincter pressure, creating a protective layer on oesophageal lesions and decreasing the frequency of transient lower oesophageal sphincter relaxations. Because of the crucial importance of gastric acid in the pathogenesis of oesophageal mucosal injury and reflux symptoms, the medical management of GORD targets primarily the control of gastric acidity. Generations of heartburn sufferers have relied on various antacid preparations to provide much-needed symptom relief. Unfortunately the “quick fix” obtained by short-term neutralisation of gastric acidity does not provide good maintenance therapy or prevent complications (Tutuian & Castell, 2003:53).

Symptom relief must be the primary aim in these patients with symptomatic GORD, and relief of heartburn and acid regurgitation should be the principal concern in clinical practice. Complete symptom relief is an attractive outcome measure in the short term. However, not all patients expect complete absence of symptoms in the long-term (Bytzer, 2003:S37).

According to Dipiro (2003b:218) the treatment of GORD is categorised into the following (see Table 2.9):

- Phase 1: Life-style changes (see table 2.8) and patient-directed therapy with antacids and/or OTC H₂RA
- Phase 2: Pharmacological interventions primarily with antisecretory agents
- Phase 3: Surgical interventions

Table 2.8: Non-pharmacological treatment with life-style modifications (Dipiro, 2003b:221).

Elevate the head of the bed 6 inches (increases oesophageal clearance).
Make dietary changes: • Avoid foods that may decrease lower oesophageal sphincter pressure (fats, chocolate, alcohol, peppermint and spearmint). • Avoid foods that have a direct irritant effect on the oesophageal mucosa (spicy foods, orange juice, tomato juice and coffee). • Include protein-rich meals in diet (augments lower oesophageal sphincter pressure). • Eat small meals and avoid eating 3 hours prior to sleeping (decreases gastric volume). • Lose weight (reduces symptoms).
Stop smoking (decreases spontaneous oesophageal sphincter relaxation).
Avoid alcohol (increases amplitude of the lower oesophageal sphincter, peristaltic waves and frequency of contraction).
Avoid tight-fitting clothes.
Discontinue, if possible, drugs that may promote reflux (calcium channel blockers, β blockers, nitrates and theophylline).
Take drugs that have a direct irritant effect on the oesophageal mucosa with plenty of liquid if they cannot be avoided (tetracyclines, quinidine, KCl, iron salts, aspirin, NSAIDs).

Life-style modifications should be started initially and continued throughout the treatment course (DeVault & Castell, 1999:1436).

The therapeutic approach to GORD is summarised in table 2.9.

Table 2.9: Therapeutic approach to GORD (Dipiro, 2003b:219).

Patient presentation.	Recommended treatment regimen.
Phase 1 Intermittent, mild heartburn.	Life-style changes PLUS Antacids (30ml 1 hour after meals and at bedtime) AND/OR Low-dose, OTC H₂RA, taken bd • Cimetidine, 200mg • Famotidine, 10mg • Nizatidine, 75mg • Ranitidine, 75mg
Phase 2 Symptomatic relief of GORD	Life-style changes PLUS Standard doses H₂RA for 6 to 12 weeks • Cimetidine 400mg, bd • Famotidine 20mg, bd • Nizatidine 150mg, bd • Ranitidine 150mg, bd OR PPI for 4 to 8 weeks • Esomeprazole 20mg/day

Table 2.9 (Continued): Therapeutic approach to GORD (Dipiro, 2003b:219).

Patient presentation.	Recommended treatment regimen.
Phase 2 (continued)	• Lansoprazole 15 to 30mg/day • Omeprazole 20mg/day • Pantoprazole 40mg/day • Rabeprazole 20mg/day
Healing of erosive oesophagitis or treatment of patients with moderate to severe symptoms or complications.	OR High doses H ₂ RA for 8 to 12 weeks • Cimetidine 400mg or 800mg, bd • Famotidine 40mg, bd • Nizatidine 150mg, qid • Ranitidine 150mg, qid
Phase 3	Anti-reflux surgery

According to Dipiro (2003b:218) the initial therapeutic modality partly depends on the patient's condition (e.g. degree of oesophagitis, presence of complications). Historically, a step-up approach had been used; starting with phase 1 and then progressing through phases 2 & 3 if necessary. If symptoms are unrelieved with life-style changes and OTC medication after 2 weeks, begin pharmacological therapy (phase 2). A step-down approach is successful in the majority of patients and decreases costs without adversely affecting quality of life (Indomi *et al.*, 2001:1098). Based on the results of an analysis conducted by Ofman *et al.* (2002:269) strategies utilising initial PPI test followed by a step-down approach may result in improved symptom relief and quality of life over 1 year. The step-down approach entails: starting with a PPI once or twice daily instead of a H₂RA and then stepping down to the lowest acid suppression needed to control symptoms (Dipiro,2003b:218). The advantages and disadvantages of step-up and step-down therapies are being compared in Table 2.10.

In a study, of patients with reflux symptoms treated with PPIs in a primary care setting, it was revealed that half could be maintained in remission without PPI therapy. Twenty-seven percent

required no medication to treat their reflux symptoms and the remaining 73% in whom step-down therapy was successful required less expensive forms of anti-GORD therapy (Indomi *et al.*, 2001:1098). Indomi *et al.*, (2001:1100) concluded in this study that it is likely that the majority of patients who require PPIs will declare themselves within the first month of step-down therapy and there are few patients who recur with symptoms requiring PPIs beyond 6 months of initial step-down therapy. Quality of life and disease severity do not seem to be adversely affected by step-down management and costs can clearly be decreased.

The findings of a meta-analysis conducted by Caro *et al.* (2001:1011) support the superiority of PPIs to H₂RAs for the acute treatment therapy of GORD. For GORD symptom relief, all five PPIs demonstrate similar efficacy after 1 to 2 weeks, but lansoprazole and esomeprazole are the only agents to demonstrate a hastening of the speed of symptom relief in head-to-head studies with other PPIs.

Table 2.10: Advantages and disadvantages of step-down and step-up treatment (Dent *et al.*, 2001:346).

Regimen	Advantages	Disadvantages
Step-down treatment (high initial therapy).	• Rapid symptom relief. • Efficient for doctor. • Avoids over investigation and associated costs.	• Potential over treatment. • Higher initial drug cost.
Step-up therapy (minimum initial therapy).	• Avoids over treatment. • Lower initial drug cost.	• Patient may continue with symptoms unnecessarily. • Takes too long. • Inefficient for doctor. • May lead to over investigation. • Uncertain end point (partial symptom relief).

Proton pump inhibitors presently constitute the most effective pharmacological means to achieve symptom resolution, healing of esophagitis and prevention of relapse in patients with GORD (Heudebert *et al.*, 2000:180; Inadomi, 2002:574). Physicians must always choose the course best suited to the individual patient and the variables that exist at the moment of the decision (DeVault & Castell, 1999:1434).

Long-term maintenance therapy should be considered to prevent complications and worsening oesophageal functions in patients who have symptomatic relapse after discontinuation of therapy or dosage reduction, including patients with complications such as Barrett's oesophagus strictures or hemorrhage. Most patients require standard doses to prevent relapses. H₂RA may be effective maintenance therapy in patients with mild disease (Dipiro, 2003b:224). In a meta-analysis conducted by Caro *et al.* (2001:1011) it was found that patients receiving PPIs had reduced relapse rates compared with ranitidine and placebo that varied from 5% to 28%. With regard to maintenance therapy, their review of individual randomised, controlled trials showed similar remission rates for lansoprazole and rabeprazole compared with omeprazole over 1 year of treatment.

According to Van Rensburg (2006) the practical guidelines used to treat GORD at Tygerberg Academic Hospital include one of the following PPIs: pantoprazole 40mg daily; omeprazole 20mg daily; rabeprazole 20mg daily or lansoprazole 30mg daily. These patients normally require long-term PPI treatment. The dose can be reduced depending on the patients' symptomatic response to alternative day therapy or by giving the patients half a dose e.g. pantoprazole 20mg.

H₂RAs are less effective for treating patients with erosive oespagitis, especially in those with severe forms of oesophagitis. High-dose H₂RAs was superior to standard dose H₂RAs in healing erosive oesophagitis (Wang *et al.*, 2005:4073). Standard dose PPIs are significantly more effective than H₂RAs in healing oesophagitis of all grades. Low-dose PPIs are not as effective as standard-dose PPIs for the healing of oesophagitis and symptom relief (Vakil & Fennerty, 2003:566). PPIs given at the recommended dose are equally effective for healing oesophagitis (Wang *et al.*, 2005:4073). In a systematic review conducted by Vakil and Fennerty (2003:566) it was found that for the healing of oesophagitis, esomeprazole is the only PPI that has been demonstrated to show superior healing in head-to-head studies with other PPIs. PPIs are the most cost effective initial and maintenance medical therapy for GORD under most circumstances. However, variations in drug acquisition costs, such as may occur in managed care practice settings, may lead to H₂RA being preferred under some circumstances (O'Connor *et al.*, 2000:3356).

For patients with GORD long-term therapeutic options include PPI therapy and antireflux surgery. According to a study conducted by Arguedas *et al.* (2004:1027) the surgical strategy is more expensive and less effective. Therefore the long-term therapy with PPIs is the preferred strategy for patients with GORD.

Bytzer (2003:S37) suggests that the long-term management options for GORD patients should include on-demand therapy. An on-demand dosing regimen is one that allows patients to take their medication *pro re nata* (as needed) if symptoms are present. The advantage of such a regimen is 2-fold: it reflects how patients actually use PPI therapy and is likely to result in cost savings compared with continuous therapy, if the total number of doses is reduced (Hughes *et al.*, 2005:1040). Remak *et al.* (2005:1512) found on-demand treatment to be less effective and more patients relapse while taking treatment on-demand compared to continuous therapy. On-demand or intermittent PPI therapy is cost effective (Inadomi, 2002:574). Rabeprazole appears to be the least expensive and cost effective PPI for on-demand therapy (Hughes *et al.*, 2005:1040; Remak *et al.*, 2005:1512). Most patients will require long-term management, for which the guiding principle is to resort to the least costly treatment that is effective in controlling symptoms (Dent *et al.*, 2001:344).

A number of novel pharmaceutical agents are currently undergoing clinical evaluation for the treatment of GORD. These include transient lower oesophageal sphincter relaxation-reduction agents, serotonergic agents/prokinetics, potassium-competitive acid blockers, mucosal protectants, histamine-3 receptor agonists and anti-gastrin agents (Vakil, 2004:1041).

2.5 ZOLLINGER-ELLISON SYNDROME

2.5.4.1 DEFINITION

A syndrome characterised by marked hypergastrinemia, gastric hypersecretion and peptic ulceration caused by a gastrin-producing tumour of the pancreas or duodenal wall (Beers & Berkow, 2004:333).

2.5.4.2 ETIOLOGY

Zollinger-Ellison syndrome is caused by gastrin-secreting gut neuroendocrine tumours (gastrinomas), which result in hypergastrinemia and acid hypersecretion (McQuaid, 2004:573).

2.5.4.3 SIGNS AND SYMPTOMS

Zollinger-Ellison syndrome typically presents as an aggressive peptic ulcer disease, with ulcers occurring in atypical locations (duodenal bulb) or after surgical treatment for presumed benign peptic ulceration (Beers & Berkow, 2004:333; McQuaid, 2004:573). Ulcers are usually solitary

but they may be multiple or occur more distally in the duodenum. Patients often present with GORD symptoms. Other symptoms include: diarrhoea, steatorrhea and weight loss. Which occur as the result of gastric acid hypersecretion. Gastric acid hypersecretion cause direct intestinal mucosal injury and pancreatic enzyme activation (McQuaid, 2004:573).

2.5.4.4 DIAGNOSIS

The diagnosis of the Zollinger-Ellison syndrome is based on elevated serum gastrin levels and elevated basal gastric acid levels (Porth, 1998:728).

2.5.4.5 COMPLICATIONS

Spontaneous perforation of the oesophagus is a rare manifestation of Zollinger-Ellison syndrome. Failure to recognise its existence can lead to an unsuccessful treatment of the oesophageal perforation (Ng *et al.*, 2001:592). Complications of perforation, bleeding and obstruction can be frequent and life threatening. (Beers & Berkow, 2004:333).

2.5.4.6 TREATMENT

According to McQuaid (2004:574) initial therapy should be directed at controlling hypersecretion. H₂RA can be used to control gastric acid secretion (Porth, 1998:728). PPIs (omeprazole, rabeprazole, pantoprazole or lansoprazole) are given at a dose of 40 to 120 mg per day, titrated to achieve a basal acid output of less than 10mEq per hour. At this level, there is complete symptomatic relief and ulcer healing (McQuaid, 2004:574). Surgical removal is indicated when the tumour is malignant and has not undergone metastasis (Porth, 1998:728).

According to Metz *et al.* (2001:3280) intravenous pantoprazole can effectively control gastric acid output for up to a week at a dose of up to 80mg three times a day. They also established that intravenous pantoprazole was well tolerated at doses of 160mg/day. In another study conducted by Metz *et al.* (2003:306) it was found that oral pantoprazole is effective and well tolerated for patients with Zollinger-Ellison syndrome and idiopathic hypersecretion. Acid output is easily controlled acutely and for up to 27 months of follow-up with a pantoprazole dose of 80 to 240 mg/day in two or three divided doses.

2.6 THE EFFECTS OF DEMOGRAPHIC AND ENVIROMENTAL FACTORS ON PREVALENCE ESTIMATES

Acid-related disorders are a great burden for patients and have significant socio-economic implications.

2.6.1 DYSPEPSIA

Age, sex and social class of patients influence the frequency of consulting a general practitioner for dyspepsia. According to Jones *et al.* (1990:404) most dyspeptic symptoms are dealt with by the patient, without seeking medical advice. The frequency of symptoms tends to fall with age, particularly in men. The proportion of dyspeptic patients seeking advice from general practitioners about their symptoms increases with age (Jones *et al.*, 1990:404; Westbrook *et al.*, 2000:1586).

Patient initiated contact with general practitioners is associated with social class. The lower social class has higher consulting rates for dyspepsia (Jones *et al.*, 1990:404). Talley *et al.* (1994:624) found that smoking, alcohol and analgesics are not important risk factors for subjects 20 to 64 years with uninvestigated dyspepsia. This is in contrast with the findings of Nandurkar *et al.* (1998:1432). In their study they found a significant association between dyspepsia and aspirin use as well as smoking.

2.6.2 PEPTIC ULCER DISEASE (PUD)

Bernersen *et al.* (1996:825) concluded in their study that non-ulcer dyspepsia and peptic ulcer have different patterns of relations to life style, social and psychological factors. They found that men were more likely to be afflicted with dyspepsia, with a small increase with age, unlike woman. This is in contrast with the statement made by Jones *et al.* (1990:404) in section 2.6.1. Non-ulcer dyspepsia occurred with a similar frequency in both sexes up to 60 years, but was less common in older people of both sexes. Peptic ulcer was seldom found up to the age of 40 years in men and 50 years in women, but in older dyspeptic patients nearly one third had peptic ulcer. Peptic ulcer was associated with a family history of peptic ulcer, smoking and daily life stress and also with poor living conditions during childhood, frequent recurrence of herpes labialis, conditions that were associated with *H.pylori* infections (Bernersen *et al.*, 1996:825). The prevalence of *H.pylori* is higher in elderly and adults (Nandurkar *et al.*, 1998:1432; Pilotto *et al.*, 2006:1541). Nandurkar *et al.* (1998:1432) also demonstrated an increased prevalence of *H.pylori* infection in men. In contrast Replogle *et al.* (1995:862) identified an increased risk for *H.pylori* among young men. Nandurkar *et al.* (1998:1432) identified an association between *H.pylori* infection and a lower income level.

2.6.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

Kulig *et al.* (2004:586) found that the main factors related to the occurrence of GORD were age, male sex, BMI (body mass index), long-standing, reflux disease and smoking. Factors associated with the longer duration of GORD included: increasing age, BMI, increasing

symptom severity, presence of erosive GORD, positive GORD family history, gender and smoking (Kulig *et al.*, 2004:587). Age and gender as confounding factors was supported in a study conducted by Shimazu *et al.* (2005:871) in a Japanese population. The overall prevalence of GORD was 5.8% and men dominated this patient population. Aging had minimal effect on prevalence in men, but the prevalence rose among women as they aged.

2.7 ACID REDUCING MEDICINE

In the following section the different acid reducing agents will be discussed with regard to their mechanism of action, therapeutic indication, adverse effects and drug interactions. According to the Snyman (2005:13a) acid reducers include the following:

- Antacids
- Antacids and combinations
- Histamine-2 receptor antagonists (H₂RA)
- Proton pump inhibitors (PPI)
- Cytoprotective agents
- Other acid reducers.

2.7.1 ANTACIDS

Antacids are simple physical agents that react with protons in the lumen of the gut. Most antacids in current use have as their principal constituent magnesium hydroxide or aluminium hydroxide, alone or in combination and occasionally in combination with sodium bicarbonate or a calcium salt (Altman, 2001:1064).

Mechanism of action

Gastric antacids are weak bases that react with gastric HCl to form a salt and water (Altman, 2001:1064).

Therapeutic indication

Antacids remain safe, simple and effective agents for the symptomatic treatment of gastric acid-related symptoms such as dyspepsia, ulcer healing, gastro-oesophageal reflux (GOR) and reflux associated with documented oesophagitis (Gibbon, 2003:40).

Adverse effects

Adverse reactions to antacids often include a change in bowel habits. Magnesium salt often causes diarrhoea while aluminium hydroxide may be constipating. Other potential problems with antacids relate to cation absorption (sodium, magnesium, aluminium, calcium) and systemic alkalosis. These become clinical problems only in patients with renal impairment. In large doses, the sodium content of some antacids may become an important factor in patients with congestive heart failure (Altman, 2001:1066).

Drug interactions

Antacids may alter the absorption of several drugs e.g. tetracycline, iron, digoxin and indomethacin. To reduce the possibility of interference with absorption, a minimum 2-hour interval between doses of the antacid and other oral medication is recommended (Gibbon, 2003:40).

2.7.2 HISTAMINE-2 RECEPTOR ANTAGONIST (H₂RA)

The four H₂RAs that are available include: cimetidine, ranitidine, famotidine and nizatidine. Cimetidine is the prototype. It seems that ranitidine, famotidine and nizatidine differ only in being less toxic than cimetidine (Trevor *et al.*, 2002:160).

Mechanism of action

H₂RA reversibly compete with histamine at H₂-receptor sites (Katzung & Julius, 2001:275). The most prominent effects of H₂RA are on basal acid secretion; less profound but still significant are suppression of acid production stimulated by feeding, gastrin, hypoglycaemia or vagal stimulation (Hoogerwerf & Pasricha, 2001:1009). The volume of gastric secretion and the concentration of pepsin are also reduced (Katzung & Julius, 2001:275).

Pharmacokinetics

According to Hoogerwerf and Pasricha (2001:1010) H₂RA are absorbed rapidly after oral administration. Peak serum concentrations are reached within 1 to 3 hours. Only a small percentage of H₂RA are protein bound. Small amounts of these drugs undergo metabolism in the liver. The kidney excretes both metabolised and unmetabolised products by both filtration and renal tubular secretion (Hoogerwerf & Pasricha, 2001:1010).

Therapeutic indication

H₂RA are capable of marked reduction in nocturnal secretion of gastric acid. They are somewhat less effective in reducing daytime secretion (Altman, 2001:1066). H₂RA are mainly used in the treatment of peptic duodenal ulcer, gastric ulcer, erosive oesophagitis (gastro-oesophageal reflux disorder; GORD) and hypersecretory conditions such as Zollinger-Ellison syndrome. Other uses of H₂RA include: hiatus hernia, stress-induced ulcers and iatrogenic ulcers (Katzung & Julius, 2001:276). Over-the-Counter (OTC) versions of H₂RA are labelled for short-term use in heartburn and dyspepsia (Altman, 2001:1067).

Adverse effects

All of the H₂RA have been generally well tolerated, with few side effects reported (Altman, 2001:1066). The most commonly reported effects are diarrhoea, dizziness, drowsiness, headache, fatigue, constipation, rash and muscle pains (Rang *et al.*, 1999:374; Katzung & Julius, 2001:276; Hoogerwerf & Pasricha, 2001:1010). Less common side effects include the central nervous system (CNS) disturbances such as confusion, delirium, hallucinations and slurred speech (these side effects occur most frequently in the elderly and in patients with impaired renal or hepatic functions), vomiting and arthralgia. Cimetidine is associated with the most adverse effects, while nizatidine seems to produce the fewest (Katzung & Julius, 2001:276).

Cimetidine is associated with confusional states, particularly in elderly patients. Cimetidine therapy may cause reversible gynaecomastia (specifically when prolonged and at high doses), impotence and a loss of libido (Gibbon, 2003:44). Cimetidine causes dose-dependent elevation in serum prolactin and may alter estrogen metabolism in men (Altman, 2001:1067).

Drug interactions

According to Gibbon (2003:44) the co-administration of cimetidine with the following drugs leads to interactions:

- Beta blockers (propranolol, metoprolol and labetalol) and lidocaine: cimetidine may potentiate their activity by reducing hepatic blood flow,
- Agents metabolised in the liver e.g. warfarin, phenytoin, theophylline, caffeine, the barbiturates, carbamazepine, diazepam, chlordiazepoxide, alprazolam, flurazepam, triazolam, sulfonylureas and tricyclic antidepressants: cimetidine inhibits several of the most important P450 drug metabolism pathways (microsomal enzymes), including those

catalysed by the 1A2, 2C9, 2D6 and 3A4 CYP isoforms. This reduces the metabolism of these agents, leading to increased effects (Katzung & Julius, 2001:276),

- Ketoconazole: absorption may be diminished significantly,
- Calcium antagonists e.g. diltiazem, nifedipine and verapamil: clearance may be diminished.

Dosage adjustments may be necessary, especially in patients with reduced kidney function (Katzung & Julius, 2001:277).

Ranitidine in ordinary therapeutic doses does not appear to inhibit the oxidative metabolism of most other drugs. All of the H₂RA except famotidine significantly increase the bio-availability of ethanol by inhibiting its gastric first-pass metabolism (Katzung & Julius, 2001:277).

2.7.3 PROTON PUMP INHIBITORS (PPIs)

Five PPIs are currently available: omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole (Snyman, 2005:13a). Omeprazole is the prototype of the PPIs (Trevor *et al.*, 2002:526). According to Vakil (2004:1041) two new PPI agents are currently in development: ilaprazole (IY-81149) and tenatoprazole. Tenatoprazole is a novel PPI with a prolonged plasma half-life (Domagala *et al.*, 2006:38).

According to Vakil and Fennerty (2003:566) no single PPI or dose has been studied head-to-head with all other agents within the class and for all clinical indications. As such, no agent or dose can be recommended as being superior for all indications for which PPIs are used based on the currently available data.

Mechanism of action

PPIs (except tenatoprazole) are substituted benzimidazole compounds that irreversibly inhibit the gastric parietal cell H⁺, K⁺-ATPase (proton pump), the terminal step in the acid secretory pathway. It markedly inhibits both basal and stimulated gastric acid secretion. It is inactive at neutral pH, but, being a weak base, accumulates in the acid environment of the canaliculi of the stimulated parietal cell (Rang *et al.*, 1999:374). Since these drugs require activation in the acid environment, they are prodrugs. They most likely act from the external side of the membrane (Altman, 2001:1067).

Tenatoprazole has been designed as a new chemical entity with a substantially prolonged plasma half-life (7 h). Tenatoprazole is characterised by an imidazopyridine backbone. The drug inhibits parietal cell H⁺, K⁺-ATPase activity in isolated hog gastric vesicles to a similar extent to omeprazole (Galmiche *et al.*, 2004:656; Domagala *et al.*, 2006:38).

Pharmacokinetics

PPIs are unstable at a low pH and are rapidly absorbed, highly protein bound and extensively metabolised in the liver by the cytochrome P450 system (particular CYP2C19 and CYP3A4). Their sulphated metabolites are excreted in the urine or faeces. Their plasma half-lives are about 1 to 2 hours, but their duration of action is much longer. Chronic renal failure and liver cirrhosis do not appear to lead to drug accumulation with once-a-day dosing of the drugs. Hepatic disease reduces the clearance of lansoprazole substantially and dose reduction should be considered in patients with severe hepatic disease (Hoogerwerf & Pasricha, 2001:1007).

The requirement for acid to activate these drugs within parietal cells has several important consequences. The drugs should be taken with or before a meal, since food will stimulate acid production by parietal cells; conversely, co-administration of other acid-suppressing agents such as H₂RA may diminish the efficacy of PPI (Hoogerwerf & Pasricha, 2001:1009).

Therapeutic indication

PPIs are used principally to promote healing of gastric and duodenal ulcers and to treat GORD that is either complicated or unresponsive to treatment with H₂RA. PPIs are also the mainstay treatment of Zollinger-Ellison syndrome (Gibbon, 2003:42).

Adverse effects

PPIs usually cause few adverse effects. The most common side effects include: nausea, abdominal pain, constipation, flatulence and diarrhoea. Other side effects involve: sub-acute myopathy, arthralgias, headaches and skin rashes (Hoogerwerf & Pasricha, 2001:1009).

Drug interactions

PPIs inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin and many other drugs. When disulfiram is co-administered with PPI, toxicity occur (Hoogerwerf & Pasricha, 2001:1009).

2.7.4 CYTOPROTECTIVE AGENTS

Cytoprotective agents enhance the mucosal protection mechanisms and/or provide a physical barrier over the surface of the ulcer (Rang *et al.*, 1999:376). Cytoprotective agents include the following: misoprostol, sucralfate and bismuth chelate (Snyman, 2004:198).

2.7.4.1 MISOPROSTOL

Mechanism of action

Prostaglandins (PGs) are synthesised in large amounts by the gastric and intestinal mucosa. PGE₂ and PGI₂ protect the deeper mucosal cells from experimental necrotic damage since they inhibit acid production by binding to EP₃ receptors on parietal cells. Prostaglandin binding to the receptor results in inhibition of adenylyl cyclase and decreased levels of intracellular cyclic AMP (Hoogerwerf & Pasricha, 2001:1011). A deficiency in prostaglandin production may contribute to ulcer formation. Misoprostol is a stable methyl analogue of PGE₁ (Altman, 2001:1068). It inhibits gastric acid secretion - both basal and that occurring in response to food - histamine, pentagastrin and caffeine by a direct action on the parietal cell. It maintains or increases mucosal blood flow and increases the secretion of mucus and bicarbonate (Rang *et al.*, 1999:376).

Pharmacokinetics

Misoprostol is rapidly absorbed and undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid (the free acid), the principal and active metabolite of the drug. Some of this conversion may occur in the parietal cells. After a single dose, inhibition of acid production can be seen within 30 minutes, peaks at 60 to 90 minutes, and lasts for up to 3 hours. Food and antacids decrease the rate of absorption of misoprostol, resulting in delayed and decreased peak plasma concentrations of misoprostol acid. The elimination half-life of the free acid, which is excreted mainly in the urine, is about 20 to 40 minutes (Hoogerwerf & Pasricha, 2001:1012).

Therapeutic indication

According to Rang *et al.* (1999:376) misoprostol is used to prevent the gastric damage that can occur with chronic use of NSAIDs.

Adverse effects

Unwanted effects are diarrhoea, with or without abdominal pain and cramps (Rang *et al.*, 1999:376; Hoogerwerf & Pasricha, 2001:1012). Misoprostol is contraindicated during pregnancy, since it can cause abortion by increasing uterine contractility (Hoogerwerf & Pasricha, 2001:1012).

Drug interactions

The co-administration of misoprostol with magnesium antacids increases the risk of diarrhoea (Gibbon, 2003:45).

2.7.4.2 BISMUTH CHELATE

Mechanism of action

Bismuth sub citrate has a high affinity for damaged tissue and forms a visible coating in the bases of ulcer craters, protecting the ulcer from gastric acid, pepsin and bile (Gibbon, 2003:46).

Pharmacokinetics

The small amount of bismuth, which is absorbed, is excreted in the urine. If renal excretion is impaired, the raised plasma concentrations of bismuth can result in encephalopathy (Rang *et al.*, 1999:376).

Therapeutic indication

Bismuth chelates are used in the treatment of duodenal and gastric ulcers (Gibbon, 2003:46).

Adverse effects

Unwanted effects include nausea and vomiting and blackening of the tongue and faeces (Rang *et al.*, 1999:376).

2.7.4.3 SUCRALFATE

Mechanism of action

In the presence of acid-induced damage, pepsin-mediated hydrolysis of mucosal proteins contributes to mucosal erosion and ulcerations. This process can be inhibited by sulphated polysaccharides (Hoogerwerf & Pasricha, 2001:1012). Sucralfate is a complex binding of aluminium hydroxide and sulphated sucrose, which, in the presence of acid ($\text{pH} < 4$), releases aluminium, acquires a strong negative charge and binds to positively charged groups in proteins, glycoproteins, etc. It forms complex gels with mucus, an action that is thought to decrease the degradation of mucus by pepsin and to limit the diffusion of hydrogen ions. Sucralfate inhibits the action of pepsin and also stimulates the mucosal-protecting mechanisms: mucus and bicarbonate secretion and prostaglandin production (Rang *et al.*, 1999:376). Sucralfate further stimulates the production of epidermal growth factor (EGF) and binds bile salts (Hoogerwerf & Pasricha, 2001:1012).

Pharmacokinetics

Sucralfate is given orally and in the acid environment of the stomach the polymerised product forms a viscous paste; 30% is still present in the stomach 3 hours after administration. A small amount is absorbed into the systemic circulation and 1 to 2% of the drug given appears in the urine (Rang *et al.*, 1999:376).

Therapeutic indication

Sucralfate is used in the prophylaxis of stress ulcers (Hoogerwerf & Pasricha, 2001:1012).

Adverse effects

The most common side effect is constipation. Less common adverse effects are dry mouth, nausea, vomiting, headaches and rashes (Gibbon, 2003:46).

Drug interactions

Sucralfate reduces the absorption of the following drugs: fluoroquinolone antibiotics, theophylline, tetracycline, digoxin, cimetidine, ketoconazole, phenytoin and amitriptyline (Hoogerwerf & Pasricha, 2001:1012; Rang *et al.*, 1999:376). Sucralfate should be taken 2 hours after the intake of other drugs (Hoogerwerf & Pasricha, 2001:1012).

Since sucralfate requires an acid environment for activation, antacids given concurrently or prior to its administration will reduce efficacy (Rang *et al.*, 1999:376). Thus antacids should not be administered within 30 minutes before or after administering sucralfate (Gibbon, 2003:45). It is recommended that sucralfate be taken on an empty stomach one hour before meals rather than after (Hoogerwerf & Pasricha, 2001:1012).

2.8 SUMMARY

In this chapter an overview of acid reducing medicine and acid-related disorders was presented.

Table 2.11: Summary of the connection between the organs, processes, disorders and medicine that play a role in acid secretion (Hoogerwerf & Pasricha, 2001:1006; Kee & Hayes, 2000:739; Vander *et al.*, 2001:571).

Organ	Process	Disorder	Medicines
Oesophagus	Lower oesophageal sphincter prevents gastric reflux into the oesophagus.	• Dyspepsia • Reflux oesophagitis (GORD)	• Antacids • H₂RAs • PPIs
Stomach	Parietal cells – Secrete hydrochloric acid (HCl). Gastrin-producing cells – Secrete gastrin.	• Dyspepsia • Peptic ulcer disease (PUD) • GORD • Zollinger-Ellison syndrome	• Antacids • H₂RAs • PPIs

Acid-related disorders present as a common problem that reduces the patients' quality of life. This chapter considers the current clinical practice with regard to dyspepsia, PUD, GORD and Zollinger-Ellison syndrome. The treatment of these disorders include: life-style modifications, OTC antacids, H₂RAs and PPIs. This literature study has shown PPIs to be the therapy of choice. Since the initial choice of treatment has a long-term impact on outcomes as well as long-term cost implications, economic evaluations of competing strategies are in demand.

CHAPTER 3:

AN OVERVIEW: PHARMACO-ECONOMICS AND DRUG UTILISATION REVIEW

3.1 INTRODUCTION

This chapter provides an overview of the concepts of managed care, drug utilisation review (DUR) and pharmaco-economics as related to this study.

There is no doubt that unrestrained utilisation of pharmaceuticals by health plan beneficiaries is financially unsustainable. Benefit management tools, such as quantity limitations, DUR, prior authorisation and various formulary programmes, may be used to reduce prescription medicine utilisation and expenditures by health plans. It is the responsibility of health care professionals and insurance benefit providers to ensure that high-quality health care for beneficiaries is not forfeited for the sake of short-term cost savings. The ultimate goal of any pharmacy benefit should be to optimise the use of pharmaceuticals in an equitable and efficient manner (Olson, 2003:266).

3.2 NATURE OF MANAGED CARE

Managed care concerns itself with quality, cost and service delivery of health-related matters including medicine usage and the provision of quality care to an enrolled patient population; tracking patient data to effectuate health care delivery and developing utilisation and outcomes parameters to educate patients. (Kiel, 2003:16).

According to Rognehaugh (1998:134) managed care can be defined as any method of health care delivery designed to reduce unnecessary utilisation of services and provide for cost control while ensuring that high quality of care or performance is maintained. Iglehart (1994:1167) is of the opinion that managed care is a system that, in varying degrees, integrates the financing and delivery of medical care through contracts with selected physicians and hospitals that provide comprehensive health care services to enrolled members for a predetermined monthly premium. All forms of managed care represent attempts to “*control health care costs*”. For this different structures and models have been developed.

3.2.1 STRUCTURES OF MANAGED CARE

According to Rognegaugh (1998:136) an MCO is a generic term that applies to a managed care plan. A managed health care plan can be defined as an employer, purchaser or insurance company, contracts with either individual providers or organised provider networks, that deliver services and may share financial risk or have some incentive to deliver quality and cost effective services (Rognegaugh, 1998:134).

Traditionally managed care was carried out in one of two basic types of organisational settings. These organisational settings include: health maintenance organisation (HMO) and preferred provider organisation (PPO).

An HMO is a prepaid organised delivery system. A fixed amount of money is available to cover the health needs of members. The organisation assumes financial risk and may transfer some of that risk to doctors or other providers through capitation. Individuals enroll with an HMO and receive health care for a fixed premium (Fairfield *et al.*, 1997).

According to Rognegaugh (1998:104) an HMO entity must have the following three characteristics:

- It must be an organised system for providing health care (ensuring health care delivery in a geographic area);
- An agreed-on set of basic health maintenance and treatment services; and
- A voluntarily enrolled group of patients.

Table 3.1 provides a few of the basic health maintenance organisations.

Preferred provider organisations act as an intermediary between the purchasers of health care and selected preferred providers, who agree to provide services on a discounted fee basis. Patients do not have to use the preferred providers in the plan but are encouraged to do so by a system of incentives and disincentives. PPOs are technically not managed care organisations. They establish a network of doctors who serve an insured population on reduced fee basis (Fairfield *et al.*, 1997).

Presently a vast majority of hybrid organisations exist, each with different health plans and options for the patient. An intensive study of these organisations, however, is outside the scope of this study.

Table 3.1: Types of HMOs (Fairfield et al., 1997; Rognegaugh, 1998:234).

Type	Description
Staff model	An HMO model that enters into a relationship with its physicians as employees. In order to provide health care to its members a premium has to be paid to the HMO, which in turn suits the providers as staff members. The staff models increasingly explore new incentive pay structures.
Group model	Doctors organise as independent groups and contract with the organisation to provide services exclusively to its enrollees.
Network model and independent practice association model	These models are now, for all practical purposes, indistinguishable. The HMO builds a network of existing practices and providers and contracts with them to provide care for the enrollees. The enrollee must choose a primary care doctor from among the network members. Providers contract with HMOs to care for enrolled patients but typically retain the right to provide services for several HMOs or fee for service patients or both.
Point of service model	Allows enrollees to seek care outside the group or network and receive partial reimbursement. Patients using point of service incur larger out of pocket expenses.

3.2.2 MANAGED CARE MODEL

The players of a managed care model are illustrated by figure 3.1. The employer (player 1) negotiates with the managed care organisation (player 2) for the most affordable rates and expansive coverage. The managed care organisation negotiates with the providers (player 3), mainly hospitals and physicians, both primary care and specialist (player 4) to gather services for its enrolled populations (additional providers are included under hospitals). The providers administer health care services to the enrolled population, patients (player 5), within the guidelines of the managed care organisation (Kiel, 2003:16). A thorough study of these models is, however, outside the scope of this study.

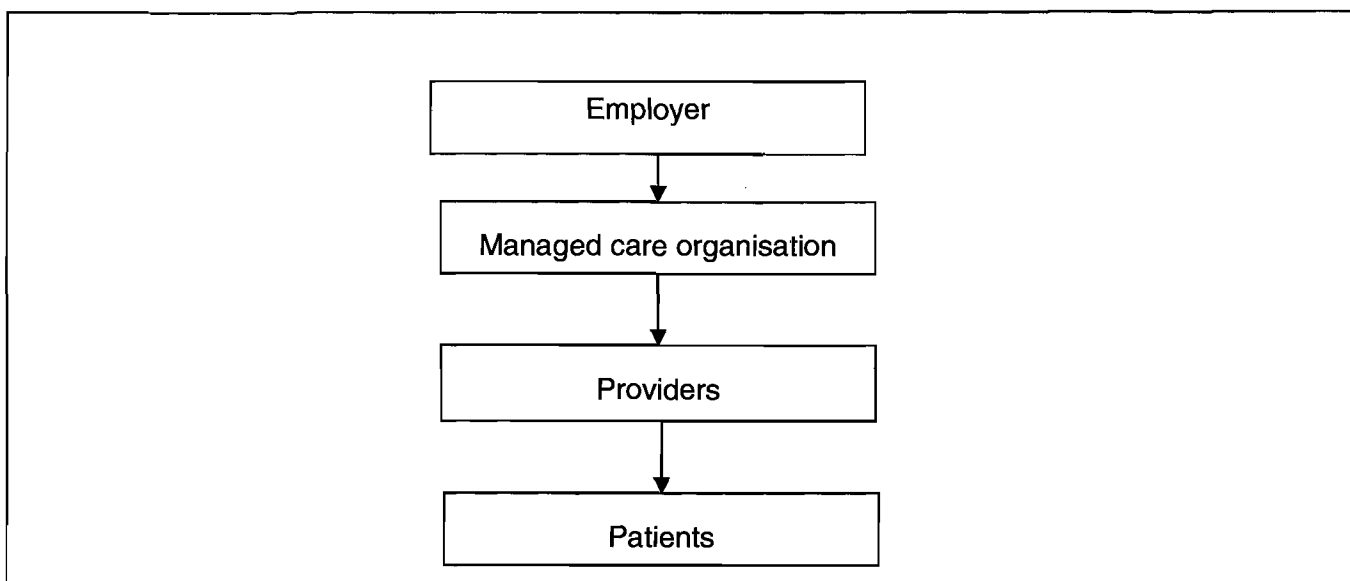


Figure 3.1: A managed care model adapted from Kiel (2003:16).

Managed care could benefit from greater use of pharmaco-economic evaluation methods to help differentiate the value of more recent and more expensive therapies (Grabowski & Mullins, 1997:543).

3.3 DRUG UTILISATION REVIEW (DUR)

The terms medicine and drug will be viewed as synonyms for the purpose of this study.

3.3.1 NATURE OF DRUG UTILISATION

The definition of drug utilisation includes all aspects of the prescribing, dispensing, administering and ingesting of drugs (Serradel *et al.*, 1987:994). The World Health Organization (WHO, 2003) elaborates on the definition: drug utilisation is the “*marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*”. These definitions of drug utilisation include the non-pharmacologic (environmental, behavioural and economic) factors influencing drug utilisation (Lee & Bergman, 1994:379).

Studies of the process of drug utilisation focus on the factors influencing and events involved in the prescribing, dispensing, administration and taking of medication. These studies include not only studies of the medical and non-medical aspects influencing drug utilisation but also the effects of drug utilisation at all levels (Lee & Bergman, 1994:379).

At institutional and regional levels these studies are referred to as drug utilisation review (DUR). A drug utilisation review is a quantitative review to establish the medical appropriateness of providers giving medications to patients for particular medical conditions (Rognehaugh, 1998:134). DUR and DUR studies are not interventions but rather activities aimed at problem detection and quantification (Lee & Bergman, 1994:380).

The U.S. Pharmacopoeia Drug Utilisation (review advisory panel) (2000:538) also stated that the goal of DUR would be to increase the appropriateness of medicine therapy by focusing on whether a specific medicine was being effectively used. The goal of DUR embraces quality control and quality assurance. Quality control relates to process-oriented criteria that measure factors such as appropriateness of dose or duration of therapy. Quality assurance relates to measuring outcomes of therapy with medicines (Erwin, 1991:596).

DUR provides the mechanism for developing standards, assessing current therapy and implementing a specific intervention followed by reassessment of drug utilisation.

3.3.2 TYPES OF DRUG UTILISATION STUDIES

Drug utilisation studies may either be quantitative or qualitative.

Quantitative studies

The objective of quantitative studies is to quantify the present state, the developmental trends and the time course of medicine usage at various levels of the health care system, whether national, regional, local or institutional (Lee & Bergman, 1994:380). It is based upon answering questions using a form of concrete measure such as numbers (Queenborough, 1999).

Qualitative studies

Qualitative studies assess the appropriateness of drug utilisation, usually by linking prescription data to the reasons for the medicine prescribing (Lee & Bergman, 1994:380).

Table 3.2 summarises the types of DUR methodologies.

Table 3.2: The three types of drug utilisation review methodologies (Wertheimer, 1988:155; Kubacka, 1996:259).

Type	Description
Retrospective reviews	Retrospective studies employ historical data. Retrospective studies are inexpensive, can be conducted rapidly and have easily accepted data. This type of DUR detects patterns in prescribing, dispensing or administering drugs to prevent recurrence of abuse or inappropriate use and serves as the framework for developing prospective standards and target interventions. Their potential for preventing problems is extremely limited since the actual review may not take place for days or weeks after an error has been made. It may be possible to prevent problems from being permanent but if the error or problem is serious or toxic, the damage will already have been done.
Concurrent reviews	Concurrent reviews are conducted during drug therapy. If a potential problem is discovered, the dispensing function comes to a halt until authorisation is received to continue as before or to initiate a modification or dosage correction. Such concurrent reviews prevent therapeutic mistakes. Concurrent review is more expensive and time consuming than retrospective studies, but has the potential for much greater pay-offs in preventing problems.
Prospective reviews	Prospective reviews are the option closest to the ideal. Use of prospective review, based upon a complete drug and medical history obtained from an interview and from historical records, permits the practitioner to evaluate the patient's pre-existing therapy on a retrospective basis and then to prevent interactions by disallowing certain drugs for a patient on the basis of a pre-existing review and by protocols already developed.

3.3.3 SOURCES OF DRUG UTILISATION DATA

According to Serradel *et al.* (1987:995) four major sources of drug utilisation data are listed below:

- Market surveys primarily based on sales data or prescription volume data

- Third-party payers or health maintenance organisations (HMO)
- Institutional and ambulatory settings
- Pharmaco-epidemiological studies designed for monitoring and evaluating exposure-related outcomes

3.3.4 THE DRUG UTILISATION REVIEW (DUR) PROCESS

In any setting, DUR can be viewed as an evolving management system applied to an underlying health care system (see figure 3.2). Each system has input (the health care system and data structure), process (criteria, application, intervention and evaluation) and output (specified percentage of decreased costs, hospitalisations or drugs per patient) components (Jones, 1991:620). There is an interrelationship between drug utilisation research and the environment in which it is conducted (Truter, 2001:4).

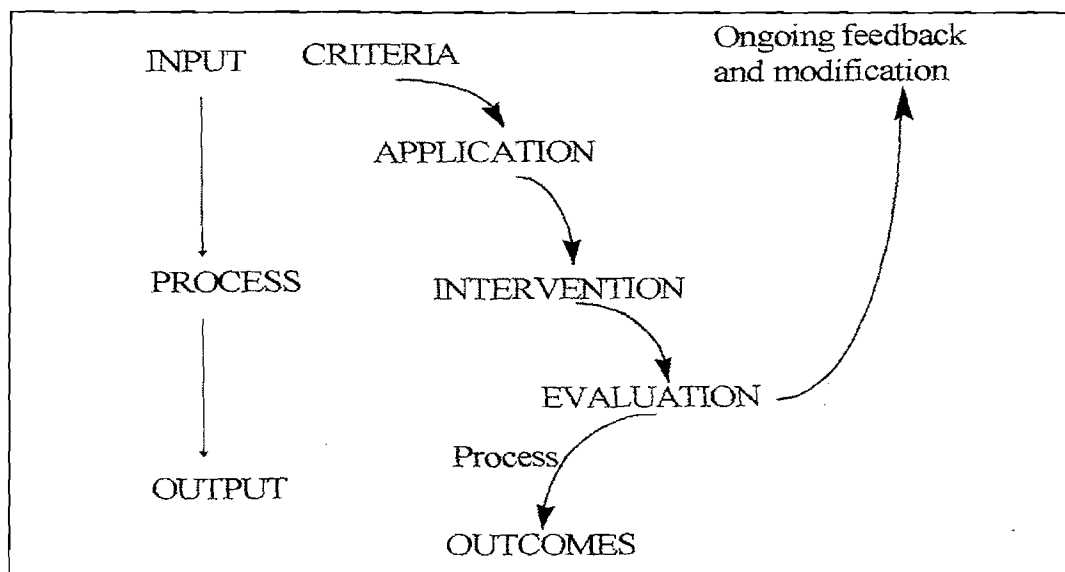


Figure 3.2: Systems view of drug utilisation review (Jones, 1991:621).

Drug utilisation review is the process by which the quality of medicine prescribing is measured against clearly determined criteria or standards. DUR is a dynamic process (see figure 3.3) aimed first at improving prescribing practices and the resulting improvement of the quality of

care and second at minimising needless expenditures (Wertheimer, 1988:154; Erwin, 1991:596; Truter, 2001:7).

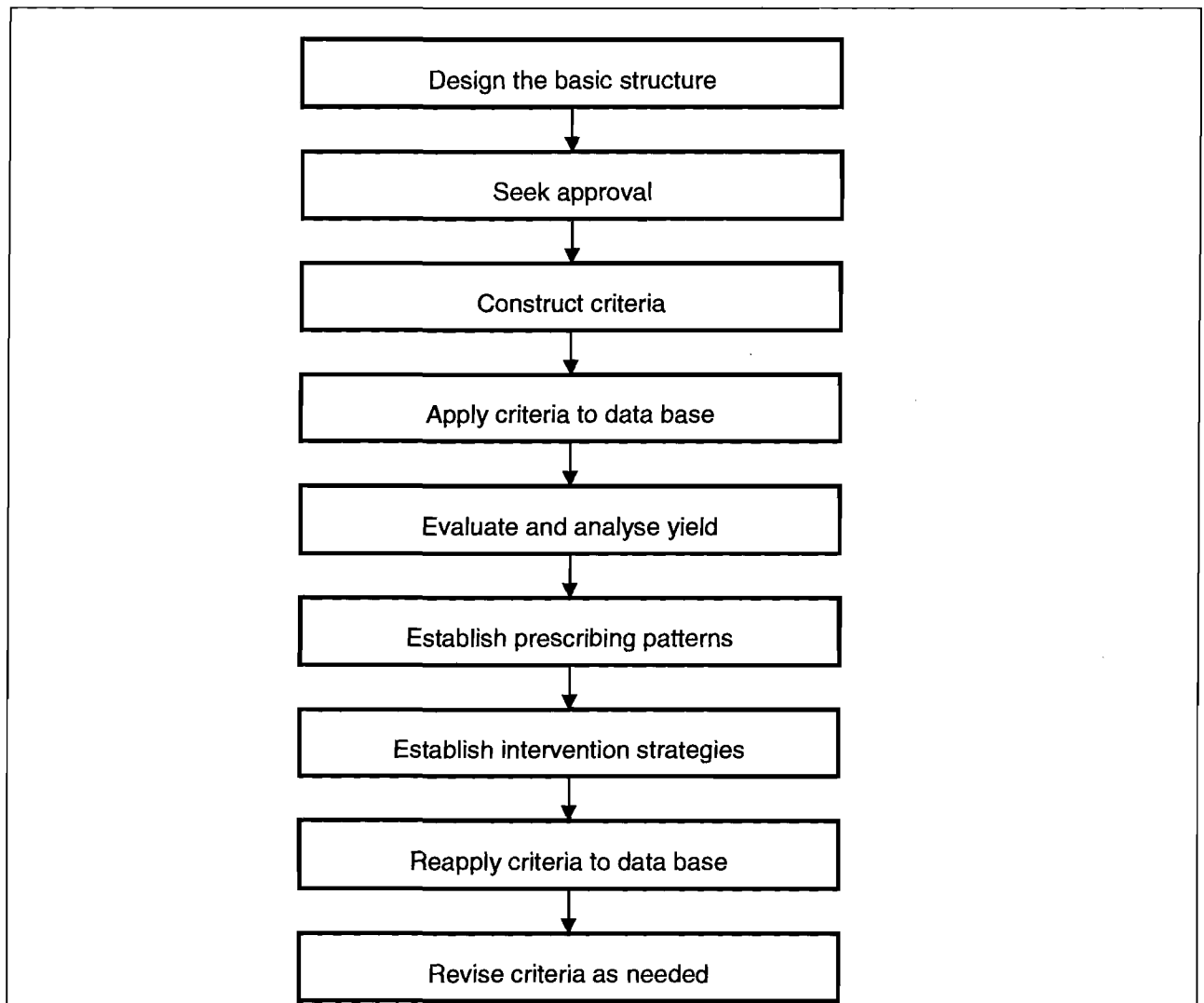


Figure 3.3: The DUR process (Erwin, 1991:596).

The DUR process has two basic components. These components consist of - data collection and analysis together with education or remedial action (Wertheimer, 1988:154).

3.3.5 UNITS OF MEDICINE MEASUREMENT

Three units for the quantification of medicine use that are predominantly used include: cost data, prescription volume and the defined daily dose (DDD) (Serradel *et al.*, 1987:994).

While prescription cost and volume may be self explainable, a brief explanation of DDD is needed. The DDD is a measure of prescribing volume maintained by the World Health Organization (WHO) based upon international prescribing behaviour (Prescribing support, 2007). DDD is a technical measuring device and defines the amount of a medicine taken by an adult who uses the medicine for its primary indication (Wertheimer, 1988:155). The DDD provides a rough estimate of the proportion of patients within a community that would receive the medicine treatment (Serradel *et al.*, 1987:995). The number of DDDs consumed is expressed by 1000 inhabitants per day when comparison is made at population level. The use of DDD has made it possible to compare the use of drugs in different areas (Sunol *et al.*, 1991:65).

According to Serradel *et al.* (1987:995) the DDD is underlined by two basic assumptions. The first assumption is that the patient is compliant and the second is that the doses used for the major indication are the average maintenance doses.

Table 3.3 provides the DDD for the different active ingredients of H₂RAs and PPIs. According to the WHO (2007b) peptic ulcer disease (PUD) (refer to section 2.5.2) and gastro-oesophageal reflux disease (GORD) (refer to section 2.5.3) are the main indication for these active ingredients

Table 3.3: The defined daily dose (DDD) for the different active ingredients H₂RAs and PPIs (WHO, 2007b).

Active ingredient	DDD	Unit	Administration route
Cimetidine	0.8	g	Oral
Famotidine	40	mg	Oral
Nizatidine	0.3	g	Oral
Ranitidine	0.3	g	Oral
Ranitidine bismuth citrate	0.8	g	Oral
Esomeprazole	30	mg	Oral
Lansoprazole	30	mg	Oral

Table 3.3 (Continued): The defined daily dose (DDD) for the different active ingredients H₂RAs and PPIs (WHO, 2007b).

Active ingredient	DDD	Unit	Administration route
Omeprazole	20	mg	Oral
Pantoprazole	40	mg	Oral
Rabeprazole	20	mg	Oral

The prescribed daily dose (PDD) is based on the actual doses prescribed by physicians for new prescriptions (Serradel *et al.*, 1987:995). It can be calculated as the ratio of two rates; which can be age- and sex- adjusted using either the group of user proportions for the year of analysis and using a direct method of standardisation. PDD is calculated per person for solid dosage forms only (Yogendran & Metge, 2004).

$$\text{PDD (Rate 1)} = \frac{\text{(Quantity of the drug dispensed} \times \text{strength of the drug) summed over year}}{\text{Number of users}}$$

$$\text{PDD (Rate 2)} = \frac{\text{Number of days supplied summed for all claims}}{\text{Number of users}}$$

$$\text{Clinical measure of PDD (Ratio)} = \frac{\text{Rate 1}}{\text{Rate 2}}$$

According to Yogendran and Metge (2004) the following formula may be use to calculate PDD if age and sex adjustment are not needed:

$\text{PDD} = \frac{\text{Total quantity} \times \text{Strength}}{\text{Total days supplied}}$
--

3.3.6 POTENTIAL CONTRIBUTION TO HEALTH CARE IN SOUTH AFRICA

In order for a medicine to be marketed, it must be shown that it is safe and that it can effectively modify the natural course of disease or alleviate symptoms when used appropriately that are for the right patient, with the right disease, in the proper dosage and intervals and for the appropriate length of time. However, used inappropriately, medicines fail to live up to their potential, with the consequent morbidity and mortality. Even when used appropriately drugs have the potential to cause harm. However, a large proportion of their adverse effects are predictable and preventable (Lee & Bergman, 1994:381). Thus drug utilisation review should be seen as one component of a quality assurance programme (Wertheimer, 1988:156).

Routinely compiled medicine statistics or drug utilisation data that are the result of such studies as can be used to estimate drug utilisation in populations by age, sex, social class, morbidity and other characteristics and to identify areas of possible over- or under-utilisation. They also can be used as denominator data for calculating rates of reported adverse drug reactions; to monitor the utilisation of specific therapeutic categories where particular problems can be anticipated (e.g. narcotic analgesics, hypnotics and sedatives and other psychotropic drugs); to monitor the effects of informational and regulatory activities (e.g. adverse event alerts, delisting of drugs from therapeutic formularies); as markers for very crude estimates of disease prevalence (e.g. digitalis utilisation for congestive heart failure, anti-parkinsonism drugs); to plan for drug importation, production and distribution and to estimate drug expenditures (Lee & Bergman, 1994:380).

Systems to limit the availability of drugs can be done at two levels namely at a national level or at a hospital level or health institution level. At a national level (also for hospital and health institution level) in South Africa drugs are registered and controlled by the South African Medicines Control Council. At hospital or health institution level a formulary system is used (Truter, 2001:20).

Pharmaco-economics and DUR are both concerned with patterns of drug consumption and their implications (Guo *et al.*, 1996:50). Drug utilisation studies provide information on costs and

effects of a drug. These studies can be used in conducting pharmaco-economic studies. The use of drug utilisation studies in conjunction with pharmaco-economic analyses may lead to more effective use of drugs and better utilisation of pharmaco-economic methods. Both will contribute to the more rational use of drugs (Sacristan & Soto, 1994:310; Truter, 1997:19).

3.4 PHARMACO-ECONOMICS

The central problem in pharmaco-economics is to find a socially acceptable solution to people's unlimited demands and society's limited ability to respond to these demands with the production of goods and services (Davey *et al.*, 1997:394). Pharmaco-economics is not primarily about saving money but rather about how one spends money and it requires consideration of a range of values including the humanitarian, ethical, cultural and financial (Jones, 2006:96).

3.4.1 NATURE OF PHARMACO-ECONOMICS

Bootman *et al.* (1991:4) defines pharmaco-economics as the description and analysis of the costs of medicine therapies to health care systems and society. According to Malek (1996:759) pharmaco-economics is the study of how people and society end up choosing to employ scarce productive resources that could have alternative uses, to produce various medicines and other pharmaceutical products and distribute them among various people and groups in society to enhance quantity and quality of life. It analyses the costs and benefits of improving patterns of resource allocation in production, distribution and consumption of such products. Thus, pharmaco-economics is a tool of management that may be applied to strategic and operational decisions about pharmaceutical development, production and consumption (Davey *et al.*, 1997:395).

Pharmaco-economics identifies measures and compares costs and consequences of medicine therapy to health care systems and society (Sanchez, 2005:1). Thus pharmaco-economics is an evidence-based approach that assesses whether the additional benefits associated with a medicine are worth the additional costs of the treatment (Jones, 2006:96).

3.4.2 PRINCIPLES OF PHARMACO-ECONOMIC ANALYSIS

The three fundamental dimensions of pharmaco-economic studies include: the perspective of the study; the types of cost and outcomes used and the type of analysis performed (Malek, 1996:759). Figure 3.4 illustrates these three dimensions.

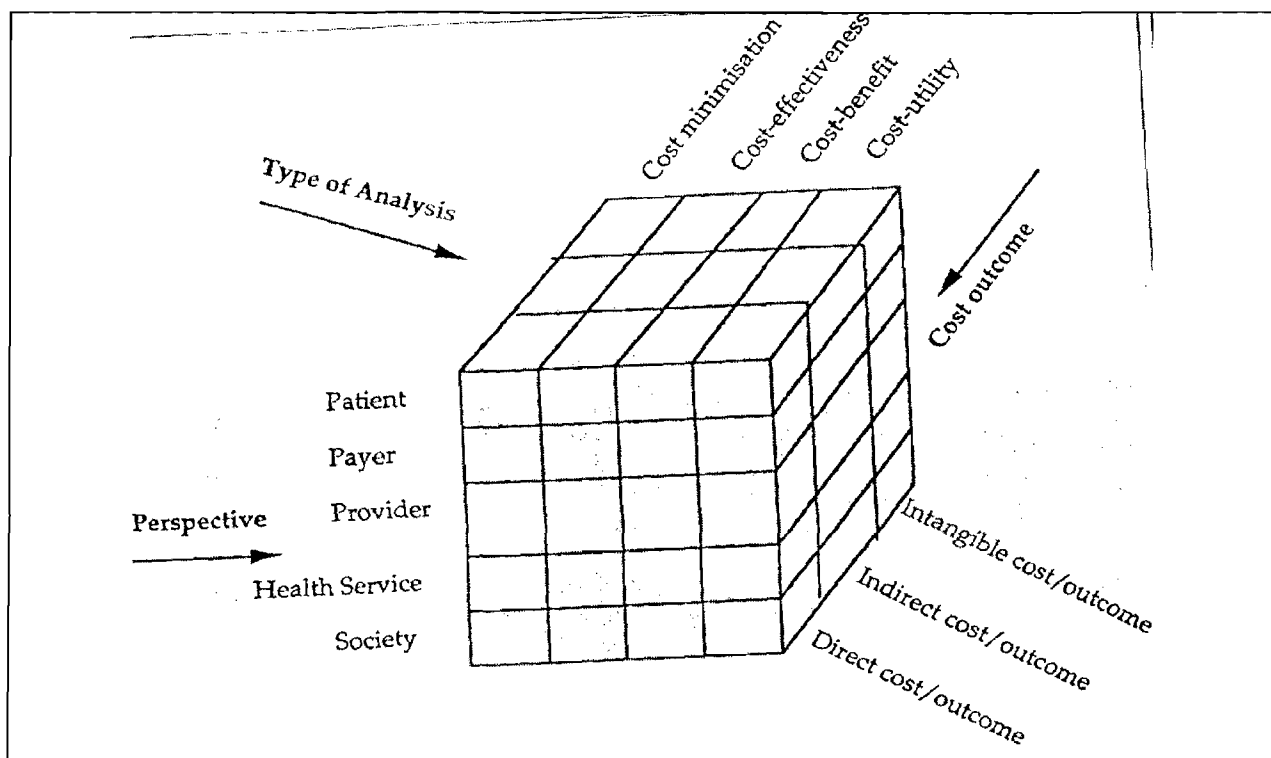


Figure 3.4: A schematic illustration of the dimensions of a pharmaco-economic analysis (Malek, 1996:759).

3.4.3 THE PERSPECTIVE OF THE STUDY

The value of a pharmaco-economic evaluation depends heavily on the perspective taken (Sanchez, 2005:2). The perspective of the study reflects the party to whom costs and benefits accrue. Perspective simply refers to who pays and who benefits. A pharmaco-economic evaluation can assess the value of a product or service from single or multiple perspectives (Sanchez, 2005:2). Analysis can be performed from the perspective of the patient, provider, insurer or society (Ellis *et al.*, 2002:272). Table 3.4 provides a summary of these common perspectives.

The perspective determines which costs and which benefits will be included in the analysis. Thus the perspective of the study has a significant influence on measured cost and benefit (Ellis *et al.*, 2002:278).

Table 3.4: Summary of common perspectives (Ellis *et al.*, 2002:278; Sanchez, 2005:2).

Perspective	Examples of costs
Patient	Patient perspective is paramount because patients are the ultimate consumers of health care services. Costs from the perspective of patients are essentially what patients pay for a product or a service. Thus the part not covered by insurance. Cost from a patient's perspective include: insurance co-payments or deductibles; travel time and time lost from work for physician visits.
Provider	Costs from the provider's perspective are the actual expense of providing a product or service. Hospitals, managed-care organisations (MCOs) or private-practice physicians are examples of providers. Costs such as drugs, hospitalisation, laboratory tests, supplies and salaries of health care professionals may be identified, measured and compared from this perspective.
Insurer/payer	Payers include insurance companies, employers or the government. Costs represent the charges for health care products and services allowed, or reimbursed, by the payer.
Society	This perspective considers the benefit to society as a whole. All direct and indirect costs are included in an economic evaluation performed from a societal perspective. Costs include patient morbidity and mortality and the overall costs of giving and receiving medical care.

3.4.4 THE TYPES OF COST

Cost is defined as the value of the resources consumed by a programme or medicine therapy of interest (Sanchez, 2005:2).

The acquisition costs are the cost to acquire a medicine or other therapy. This cost may represent the wholesale price, retail price or co-payment to the patient. The appropriate acquisition cost will depend on the perspective of a particular analysis (Ellis *et al.*, 2002:272).

Pharmaco-economic analysis classifies cost into direct, indirect and intangible costs (Malek, 1996:760).

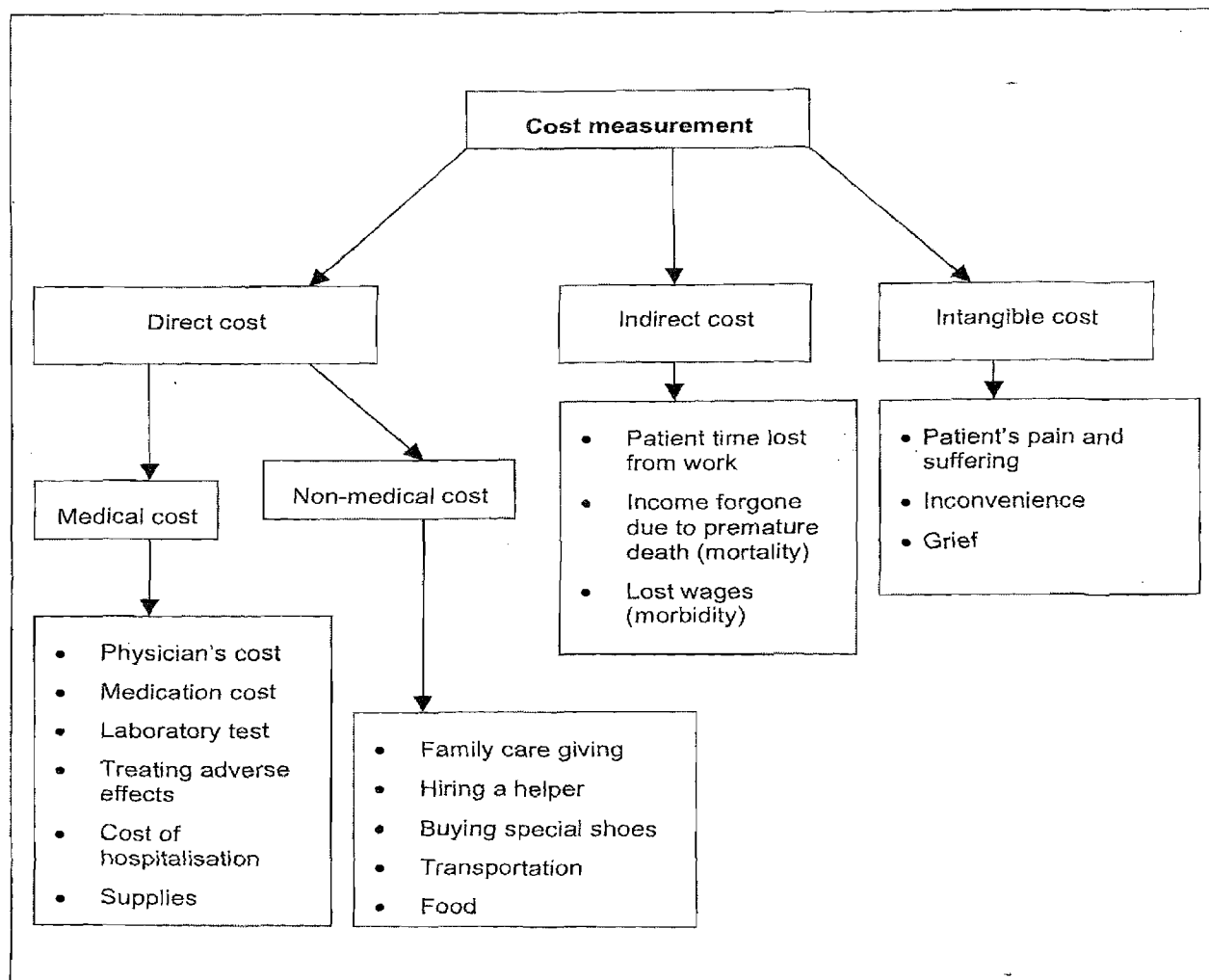


Figure 3.5: Classification of cost adapted from Ellis *et al.* (2002:279), Malek (1996:761) and Sanchez (2005:3).

According to Malek (1996:761) direct costs are the costs of the resources used in a specific medical intervention. Thus direct cost is associated directly with the delivery of medical care and the purchasing of drugs out of the pocket (Freund & Dittus, 1992:24). These costs can easily be identified, measured and valued. Direct costs can be subdivided into medical and non-medical cost (refer to figure 3.5).

Direct medical costs consist of fixed and variable costs. Fixed costs are not readily influenced at the treatment level and remain relatively constant. Examples of fixed cost include heat, rent and electricity. Variable costs changes as a function of volume and include medications, fees for professional services and supplies (Sanchez, 2005:3).

Indirect costs are associated with the loss of earnings and the loss in finance and production resulting from illness (Malek, 1996:761).

Intangible costs are those of other non-financial outcomes of disease and medical care (Sanchez, 2005:3). Intangible costs are associated with the patient's pain and suffering (Malek, 1996:761).

Opportunity and incremental costs are often other costs discussed in pharmaco-economic evaluations. Opportunity costs represent the economic benefit forgone when using one therapy instead of the next best alternative therapy. Incremental costs represent the additional cost that a service or treatment alternative imposes over another compared with the additional effect, benefit or outcome it provides (Sanchez, 2005:4).

3.4.5 OUTCOME MEASUREMENT

Outcomes can be categorised into the following categories: economic, clinical and humanistic. Economic outcomes are the direct, indirect and intangible costs compared with the consequences of medical treatment alternatives. Clinical outcomes are the medical events that occur as a result of disease or treatment (e.g. safety and efficacy end points). Humanistic outcomes are the consequences of disease or treatment on patient functional status or quality of life along several dimensions. These dimensions can include one of the following: physical function, social function, general health and well-being and life satisfaction (Sanchez, 2005:4).

The outcomes of a study can be positive or negative. A positive outcome is the desired effect of a drug. Possibly manifested as cases cured, life-years gained or improved health-related quality of life (HRQOL). A negative outcome is an undesired or adverse effect of a drug. Negative outcomes are manifested as a treatment failure, an adverse drug reaction (ADR), a drug toxicity or death (Sanchez, 2005:4).

Outcomes can also be discussed in terms of intermediate and final outcomes. Intermediate outcomes serve as a proxy for more relevant final outcomes (Sanchez, 2005:4).

It is in these component outcomes that the differences arise among cost-effectiveness, cost-benefit and cost-utility analysis (Ellis *et al.*, 2002:279).

3.4.6 THE TYPE OF ANALYSIS PERFORMED

Pharmaco-economic studies include: cost-of-illness, cost-minimisation, cost-effectiveness, cost-benefit and cost-utility analysis. Each of these types of analyses differs in what it measures and under what circumstances its use is appropriate (as summarised by table 3.5).

Table 3.5: Summary of pharmaco-economic methodologies (Freund & Dittus, 1992:30; Sanchez, 2005:5).

Description	Application	Limitation
Cost-minimisation analysis		
Finds the least expensive cost alternative with equal benefits.	Use when benefits are the same.	Frequently confused with CEA; difficult to establish clinically identical effectiveness across
Cost-benefit analysis		
Measures benefit in monetary units and compute a net gain.	Can compare programmes with different objectives.	Valuing benefits in monetary units is difficult and not widely accepted.
Cost-effectiveness analysis		
Compares alternatives with therapeutic effects measured in physical units and computes a cost effectiveness ratio.	Can compare drugs/programmes that differ in clinical outcomes and use the same unit of benefit.	Cannot compare across different types of programmes.
Cost-utility analysis		
Measures therapeutic consequences in utility units rather than physical units; computes a cost-utility ratio	Used to compare drugs/programmes that are life extending with serious side effects or those producing reductions in morbidity.	Difficult to measure utilities.

Table 3.5 (Continued): Summary of pharmaco-economic methodologies (Freund & Dittus, 1992:30; Sanchez, 2005:5).

Quality of life		
Physical, social and economic aspects of patient's well-being that are relevant and important to the patient.	Examines drug effects in areas not covered by laboratory or physiologic measurements.	Assumes preferences towards health states do not change over time.

Cost-of-illness

Ellis *et al.* (2002:272) define cost-of-illness as an accounting of the costs associated with an intervention with no consideration of outcomes. Cost-of-illness estimates the cost of a disease on a defined population (Sanchez, 2005:5). Thus cost-of-illness analysis provides a common framework through which to assess the potential for developing a medicine to treat a particular disease (Bonk, 1999:25).

One cannot make any comparison among treatments by means of a cost-of-illness analysis because no consideration is given to the relative effectiveness of each of the therapies. One of the treatments may be more expensive, yet may produce a better outcome. Without considering treatment outcomes, cost information can be misleading as a guide to resource allocation decisions (Ellis *et al.*, 2002:273).

Cost-minimisation analysis (CMA)

Cost-minimisation analysis is conducted when the outcomes or consequences of two or more interventions have been determined to be equal. The CMA allows one to evaluate only the inputs or costs of each alternative. For example, if two antibiotics have been found to be equally effective for the treatment of *Helicobacter pylori* – with equal cure rates, adverse reactions, complications and durations of therapy – simply comparing their acquisition costs would be appropriate (Jolicoeur *et al.*, 1992:1741). Thus a cost-minimisations study would determine all costs associated with each of the treatments to determine which treatment would be the least expensive assuming equal outcomes (Ellis *et al.*, 2002:274).

Cost-minimisation analysis is not commonly used to assess medicine therapies, programmes or services because of the strict requirements of therapeutic equality. This method, however, can be useful for assessing the cost difference among dosage forms of the same medicine or

among generically equivalent medicines for which patient outcomes have been shown to be the same (Jolicoeur *et al.*, 1992:1741).

Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis is a comparison of the cost per standardised unit of effectiveness for two or more interventions that provide varying outcomes (Ellis *et al.*, 2002:272). This is accomplished through the selection of a standardised measure of effectiveness (Ellis *et al.*, 2002:274). In this type of analysis the outcome is common to all the alternatives but different programme have different success rates in achieving it (Malek, 1996:761). The clinical effects of alternative therapies (e.g. years of life saved, cases cured, life expectancy or drop in blood pressure) are compared to their net costs (McCombs, 1998:114S; Sanchez, 2005:6).

When a treatment is more effective and less expensive or less effective and more expensive - the choice is obvious. The preferred treatment strategy is called the dominant strategy (see figure 3.6). In this case a cost-effectiveness comparison is unnecessary. However, when one treatment is more effective but also more expensive, cost-effectiveness ratio helps quantify the clinical and economic consequences of using it (Ellis *et al.*, 2002:274).

		COST	
EFFICACY		Strategy 1 < Strategy 2	Strategy 1 > Strategy 2
	Strategy 1 > Strategy 2	Strategy 1 is dominant; cost-effectiveness study unnecessary.	Incremental cost-effectiveness study useful.
	Strategy 1 < Strategy 2	Incremental cost-effectiveness study useful.	Strategy 2 is dominant; cost-effectiveness study unnecessary.

Figure 3.6: Schematic representation of efficacy vs. cost (Ellis *et al.*, 2002:275).

Cost-effectiveness analyses are often used to examine alternative therapies for a single disease. The cost effective ratio can either be expressed as an average cost-effectiveness ratio (ACER) or as an incremental cost-effectiveness ratio (ICER). The incremental cost-effectiveness ratio (see figure 3.7 for formula) refers to the amount of money needed to produce an additional benefit and decide whether the extra benefits are worth the extra cost (Freund & Dittus, 1992:23; Ellis *et al.*, 2002:275). The average cost-effectiveness ratio (see figure 3.4 for formula) represents the total cost of a programme or treatment alternative divided by its clinical outcome to yield a ratio representing the dollar cost per specific clinical outcome gained (Sanchez, 2005:6).

$\text{ACER} = \frac{\text{Health care cost (R)}}{\text{Clinical outcome (natural units)}}$	$\text{ICER} = \frac{\text{Cost of drug A} - \text{Cost of drug B (R)}}{\text{Benefits of drug A} - \text{Benefits of drug B (natural units)}}$
---	---

Figure 3.7: Summary of formula for average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER).

Using these ratios, the clinician would choose the alternative with the least cost per outcome gained. The most cost effective alternative is not always the least costly alternative for obtaining a specific therapeutic objective (Sanchez, 2005:6).

According to McCombs (1998:114S) the limitation of this approach is that all years of life are valued equally without adjustments for the quality of life enjoyed by the patient. Society values a year of life at full function higher than all years of life in a comatose state.

Cost-benefit analysis (CBA)

Cost-benefit analysis is a comparison of the costs and benefits of two or more interventions that provide varying outcomes, where outcomes are measured in money terms (Ellis *et al.*, 2002:272). This is a controversial approach because it requires valuation in money terms of survival and quality of life, as well as valuation of the loss of eyesight, kidney failure, hearing impairment and many other outcomes of medical intervention (Malek, 1996:761).

According to Jolicoeur *et al.* (1992:1742) CBA allows a pharmacy department to compare the costs and benefits of initiating an antimicrobial-monitoring service (outcome = number of

treatment successes) with those of a hepatitis B vaccination programme (outcome = number of hepatitis B cases avoided).

A clinical decision maker would choose the programme or treatment alternative with the highest net benefit or the greatest benefit-to-cost (B/C) ratio. If the B/C ratio is greater than 1, the programme or treatment is of value. The benefits realised by the programme or treatment alternative outweigh the cost of providing it. If the B/C ratio equals 1, the benefits equal the cost. The benefits realised by the programme or treatment alternative are equivalent to the cost of providing it. If the B/C ratio is less than 1, the programme or treatment is not economically beneficial. The cost of providing the programme or treatment alternative outweighs the benefits realised by it (Sanchez, 2005:5). A cost-benefit analysis of a single therapeutic programme can determine whether that programme is economically worthwhile in its own right. A worthwhile programme is one in which the benefits exceed the costs (Ellis *et al.*, 2002:278).

This pharmaco-economic method is particularly useful when resources are limited and only one programme can be implemented (Jolicoeur *et al.*, 1992:1742). However, CBA is not common in the evaluation of pharmaceuticals because of valuation problems and willingness to pay. Market valuation and professional assessment have been used for this purpose, although most of the published studies are rather dated (Malek, 1996:761).

Cost-utility analysis (CUA)

Cost-utility analysis is a version of CEA in which outcomes are measured using patient-centred instruments. Medicine therapies are compared in terms of their costs per unit of patient benefit (Malek, 1996:761).

According to Malek (1996:761) the health impact of a treatment has two dimensions, i.e.

- A quantity improvement (adding years to life); and
- A quality improvement (adding life to years).

Drugs can be compared in terms of the cost of the extra survival they give the average patient affected by a life-threatening disease (Malek, 1996:761).

According to Ellis *et al.* (2002:272) CUA is a comparison of the cost per quality-adjusted life-year (QALY) for two or more interventions that provide varying outcomes. A QALY is computed as a year of life saved or free from disease, multiplied by the utility score. The utility score is expressed on a scale of 0 to 1 (Ellis *et al.*, 2002:277). For example, a full year of health in a

disease-free patient would equal 1.0 QALY, whereas a year spent with specific disease might be valued significantly lower, perhaps as 0.5 QALY, depending on the disease (Sanchez, 2005:6).

Cost-utility analysis is more complicated than cost-effectiveness analysis because it involves the actual measurement of individuals' preferences (Ellis *et al.*, 2002:277).

Table 3.6 provides a comparison of the different types of a pharmaco-economic analysis as related to the cost and outcome.

Table 3.6: Comparison of the types of a pharmaco-economic analysis as related to the cost and outcome (Sanchez, 2005:5).

Type	Cost measurement	Outcome measurement
Cost-minimisation analysis	Money terms	Assume to be equivalent
Cost-benefit analysis	Money terms	Money terms
Cost-effectiveness analysis	Money terms	Natural units
Cost-utility analysis	Money terms	QALYs

According to Malek (1996:761) CEA is the most popular type of study of the four, mostly because such an analysis provides a chance of head to head comparison of drugs for companies who see a comparative advantage for their own brands and would like to justify premium prices for their products.

3.4.7 EXAMPLES OF PHARMACO-ECONOMIC STUDIES AS RELATED TO ACID-RELATED DISORDERS

In this section the focus will be on the provision of examples of pharmaco-economic studies that have already been done in practice. These studies will be categorised according to the type of analysis performed.

Cost-of-illness

The results of a cost-comparative study indicate that, over a 1-year period, initial treatment with PPIs costs 20% less than initial treatment with branded H₂RA and costs 3% more than initial

treatment with a generic H₂RA. From a purely economic standpoint, treating GORD initially with PPIs is less costly than treating initially with H₂RA (Zagari *et al.*, 1995:254).

Cost-minimisation analysis (CME)

In a cost-minimisation analysis conducted by Kivioja *et al.* (2004:176) it was assumed that the effectiveness of PPI therapy depended on the length of the holding time of the intragastric pH. If the dosages that had holding times (pH > 4) of 11 hours or more in a 24-hour period were included, the least expensive drug therapy would be lansoprazole. If only the dosages that had holding times of 12 hours or 13 hours or more in 24-hour period were included, the least expensive drug therapy would be rabeprazole. Omeprazole and esomeprazole would be the most expensive drug therapies. Kivioja *et al.* (2004:177) concluded that, considering the holding times, the most cost effective low-dose PPI therapies were rabeprazole 10mg and esomeprazole 20mg.

Cost-effectiveness analysis (CEA)

Treating healed GORD with maintenance PPI only after a patient had experienced two further recurrences (no maintenance until a second recurrence) is the least effective and least costly approach. Waiting to initiate maintenance therapy until symptoms recur once is more effective and more costly. Treating with maintenance PPI from the beginning is the most effective and most costly approach. Initial maintenance appears to be cost effective if symptoms of GORD cause at least 22% decrease in quality of life. Withholding maintenance until the time of a first recurrence, appears to be cost effective if symptoms of oesophagitis cause only a 2% decrease in quality of life (Harris *et al.*, 1997:85).

A 1-year study comparing the cost effectiveness of omeprazole 20mg once daily, omeprazole 10mg once daily or ranitidine 150mg twice daily as initial therapy in an intermittent treatment strategy for GORD showed no statistically significant difference between the alternatives at the end of the study period. The results of this study give no support to the notion that a step-up approach in intermittent treatment of patients with symptomatic GORD will result in cost saving and be cost effective (Stalhammar *et al.*, 1999:495).

The objective of a study conducted by Ofman *et al.* (2000:906) was to compare the cost effectiveness of rabeprazole and ranitidine in acute and maintenance therapy for erosive oesophagitis using symptom response, rather than endoscopic healing, as the clinical outcome. A decision analysis was used to model the cost effectiveness of competing therapies based on the results of clinical trials of rabeprazole versus ranitidine and estimates from the medical

literature. This analysis demonstrates that management of oesophagitis with rabeprazole is more effective and may be more cost effective than management with generic ranitidine, despite rabeprazole's higher per-unit cost.

In a cost-effectiveness analysis conducted by Wahlqvist *et al.* (2002a:273) it was found that on-demand treatment with esomeprazole 20mg is cost effective compared to conventional omeprazole strategies in patients with GORD. The results showed that after a 6-month treatment, 90% of patients could control symptoms effectively with on-demand esomeprazole 20mg. The expected number of relapses per patient was estimated at 0.10 for on-demand esomeprazole, 0.57 to 1.12 for intermittent omeprazole and 0.47 to 0.75 for conventional omeprazole treatment. The esomeprazole strategy incurred considerably lower direct medical costs (16 to 61%) than either omeprazole strategies.

In another study Wahlqvist *et al.* (2002b:283) estimated the healing rate after 4 weeks to be 77.7% in esomeprazole 40mg once-daily recipients, compared with 67.6% in omeprazole 20mg once-daily recipients. The corresponding values after 8 weeks' treatment were 93.4% and 86.2%. Esomeprazole 40mg once daily produces a total cost saving of 14.3% compared with omeprazole 20mg once daily. Esomeprazole 40mg once daily is remains cost effective even when the cost of omeprazole 20mg once daily is considerably reduced. Thus esomeprazole provides greater effectiveness at a lower cost in the treatment of patients with reflux oesophagitis.

In a cost-effectiveness analysis performed by Erstad (2004:1281) it was found that high-dose intravenous PPI in conjunction with therapeutic endoscopy is the most cost effective approach for the management of hospitalised patients with acute peptic ulcer bleeding. The purpose of this study was to compare the cost-effectiveness of adjunctive oral and intravenous PPIs. Hospitalisation without concomitant PPI therapy was the most costly scenario in this study.

Cost-utility analysis (CUA)

Treatment with generic omeprazole was the least costly over a year. Since it also resulted in a higher number of symptom-free days and QALYs gained than branded lansoprazole, branded esomeprazole and branded omeprazole. Pantoprazole was more effective than generic omeprazole, but was less effective and more costly than rabeprazole. Treatment with rabeprazole resulted in the most symptom-free days and QALYs gained. It also cost less over one year than the other PPIs, due to the lower number of relapses and the lower need for referrals and endoscopies. Therefore rabeprazole is the treatment of choice for GORD as it is less costly and more effective than other PPIs (Remak *et al.*, 2005:1511).

3.4.8 STEPS IN PHARMACO-ECONOMIC RESEARCH

Table 3.7 describes the basic steps for conducting a pharmaco-economic analysis.

Table 3.7: Steps in pharmaco-economic research (Jolicoeur *et al.*, 1992:1742; Bonk, 1999:88; Sanchez, 2005:11).

Steps	Description/Examples
<i>Step 1:</i> Define the study objective.	The general objective of this study is to review the prescribing patterns and cost of acid reducing medicine (refer to section 4.2).
<i>Step 2:</i> Determine the research perspective.	The perspective of a pharmaco-economic evaluation may be patient, provider, payer and insurer (refer to table 3.3). The point of view determines the scope of the analysis and the data required. For the purpose of this study the perspective is of the insurer/payer.
<i>Step 3:</i> Identify any alternative agents and treatment alternatives.	All likely treatment options should be identified and investigated. Alternative agents include antacids, H ₂ RA and PPIs. Treatment alternatives can consist of pharmacological and non-pharmacological options but should be clinically relevant.
<i>Step 4:</i> Measure outcomes as appropriate to the perspective.	The outcomes identified should include both positive and negative clinical outcomes (refer to section 3.4.5).
<i>Step 5:</i> Identify the appropriate pharmaco-economic method to employ.	Pharmaco-economic methods to choose from include: CMA; CBA; CEA and CUA (see section 3.4.6).
<i>Step 6:</i> Place monetary values on the outcomes.	The outcomes then have to be given rand values. Placing a monetary value on treatment alternatives and outcomes includes not only drug administration and acquisition costs but also cost of positive and negative clinical outcomes (e.g. determining the costs of adverse drug reactions and treatment failures).
<i>Step 7:</i> Calculate summations and ratios of costs versus outcomes.	Were costs and outcomes meaningfully summed? The use of decision analysis can assist in conducting various economic evaluations, including CEA.

Table 3.7 (Continued): Steps in pharmaco-economic research (Jolicoeur *et al.*, 1992:1742; Bonk, 1999:88; Sanchez, 2005:11).

Steps	Description
<i>Step 8:</i> Discount costs or conduct sensitivity analysis of research assumptions.	When the costs and benefits of a programme extend over time, the future costs and benefits should be discounted to reflect their present value. Sensitivity analysis is used to determine what impact assumptions have on study results.
<i>Step 9:</i> Interpret and disseminate the findings of the research study.	The conclusions of a pharmaco-economic analysis must relate clearly, concisely and accurately to step 1.

Ultimately, economic analyses remain models of the anticipated consequences of alternative decisions. Although such models are capable of facilitating decision making, the responsibility of individuals for making decisions is not diminished. Nevertheless, the power of the analytical techniques provides simple justification for those faced with resource allocation decisions to come to terms with the principles of economic analysis (Freund & Dittus, 1992:28).

3.5 CHANGES IN SOUTH AFRICAN HEALTH CARE

Generic substitution, prescribed minimum benefits (PMB) and the single exit price (SEP) are examples of changes that occurred in the South African health care market during the past years. These changes bear relevance to this study.

3.5.1 GENERIC SUBSTITUTION

Generic medicines are equivalent to the brand name (innovator) medicines (refer to section 5.2.4 & 5.2.5). They contain the exact same active ingredient, strength and dosage form as the original product (Mestern, 2003:2). Generic medicines are produced after the patent on an original medicine has expired. Other manufacturers are then entitled to copy the original product using the same active ingredients as contained in the original medicine. Generic medicines are much less expensive because the generic manufacturers do not have to invest in the costly and extensive research usually required before original medicines are manufactured. Also, once generic drugs enter the market, there is greater competition, which keeps the price down (CDER, 2007a).

The regulations regarding generic substitution appear in The Medicines and Related Substances Act (101/1965) as amended (the medicines act).

The new legislation on generic medicine came into effect on 2 May 2003 (Du Toit, 2003:4). The pharmacist is now compelled to inform all patients of the benefits of the substitution of a branded medicine with a generic medicine. Once the pharmacist has informed the patient of the benefits of generic substitution, the generic medicine must be dispensed unless expressly forbidden by the patient. If the patient refuses a generic medicine the pharmacist must make a note of this fact on the prescription. It is important to note that the pharmacist or person dispensing the prescription must not dispense a generic medicine, if the prescriber has written in his/her own hand on the prescription, next to the items prescribed, that “no substitution” of that item may take place and if the retail price of the generic medicine is higher than the price of the branded product or if a medicine has been declared non-substitutable by the Medicines Control Council (MCC) (South Africa, 2003a:MAE30).

3.5.2 PRESCRIBED MINIMUM BENEFITS (PMB)

On, 1 January 2004, the new medical scheme legislation became effective (Mediscor, 2007). This legislation entails that medical schemes are obligated to pay for an exclusive list of 270 conditions or group of conditions. These conditions were specified in Annexure A of the Regulations to the Medical Schemes Act (131/1998). Included in this list is the chronic disease list (CDL). The benefits for the 270 conditions and the 27 identified chronic diseases (CDL) are known as PMBs. PMBs are benefits in respect of relevant health services prescribed by regulations under the act, and consists of 27 identified chronic conditions that constitute the chronic disease lists (CDL) according to the South African Medical Schemes Act (Act 131 of 1998). Each condition has a detailed “*treatment protocol*” that has been published in the Government Gazette. The objectives of the PMBs are to: avoid incidents where individuals lose their medical scheme cover in the event of serious illness and the consequent risk of unfunded utilisation of public hospitals; and to encourage improved efficacy in the allocations of private and public health care resources.

Acid-related disorders, however, are not among the 27 chronic disease conditions (South Africa, 2003b:4).

3.5.3 SINGLE EXIT PRICE (SEP)

The whole purpose of the Medicine Control Amendment Act of 1997 is to make medicines affordable to the people of our country and to improve practices relating to the manufacture and

sale of medicines (Tshabalala-Msimang, 2004:5). Central to the regulations relating to a Transparent Pricing System for Medicines and Scheduled Substances is the SEP. The SEP came into effect on 2 August 2004. Manufacturers or importers are required to set a price, called the SEP, at which a particular medicine has to be sold to any person other than the State (South Africa, 2004:6). A maximum is established for the original exit price and this price may only be increased once a year, while it may be reduced any number of times. The law also requires that the SEP be printed on all containers dispensed (South Africa, 2005:8).

According to the regulations, persons dispensing medicines are not allowed to add a mark-up to the SEP, but have to charge a professional service fee or dispensing fee instead. Depending on the schedule and the provider specialty a maximum level is set for the dispensing fee. A series of dispensing fees were already proposed. Table 3.8 gives an example of the dispensing fees published in the Government Gazette on 30 April 2004.

Table 3.8: The maximum level set for the dispensing fee (South Africa, 2004:6).

Schedule & Provider specialty	Dispensing fee
Schedule 0	• Mark-up can be charged but it may not exceed the percentage mark-up that was applicable before 2 May 2004.
Schedule 1 & 2 dispensed by a pharmacist without a prescription.	• 16 % for products with an SEP less than R100. • R26 for products with an SEP of R100 or more.
Schedule 1 to 8 products dispensed by a pharmacist in terms of a prescription.	• 26 % for products with an SEP less than R100. • R26 for products with an SEP of R100 or more.
Charged by a doctor.	• 16 % for products with an SEP less than R100. • R16 for products with an SEP of R100 or more.

The introduction of the medicine pricing regulations in 2004 led to a court challenge by retail pharmacies, Pharmaceutical Society of South Africa (PSSA) and the Pharmaceutical Manufacturers Association (PMA). The matter was heard in the Cape High Court, Supreme Court of Appeal and ended in the Constitutional Court. The Supreme Court of Appeal (SCA) ruled on 20 December 2004 in favor of the PSSA and its partners. The SCA agreed that the pricing regulations should be set aside and that the Department of Health should pay all the legal costs. This emphasised the need for the revision of the dispensing fee (Bester & Hammann, 2005). The Constitutional Court judgment of 30 September 2005 declared that the dispensing fee regulations were invalid. The court recommended that the Pricing Committee reconsider the fee of 26 % of an SEP capped at R26 (refer to table 3.7) (Tshabalala-Msimang, 2006). The effect of the judgment was that the regulated SEP and the dispensing fee was no longer in operation. Pharmacists and doctors could now charge any fee that would cover the costs of dispensing (Bester & Hammann, 2005).

Table 3.9 gives the dispensing fee for pharmacists as announced on 31 October 2006.

Table 3.9: The dispensing fees as announced on 31 October 2006 (Tshabalala-Msimang, 2006).

Single exit price (SEP)	Dispensing fee
< R75	• 33 % of SEP plus R4
≥ R75 up to < R250	• 6 % of SEP plus R25
≥ R250 up to < R1000	• 3 % of SEP plus R33
≥ R1000	• 1.5 % of SEP plus R50

The latest update on the dispensing fee process is that the Pharmacy Stakeholder's Forum (PSF) is still engaged in seeking resolutions to the problem of the quantities of the published dispensing fee (PSSA, 2007). Thus pharmacists and doctors are still charging any fee that would cover the costs of dispensing.

According to the Board of Health care Funders (2006) the new dispensing fee structure will discourage the inappropriate use of high cost products, thereby making medical scheme contributions more affordable and assisting government and funders in making private health care accessible to more South Africans.

3.6 SUMMARY

Since health care expenditures increase continually the economic aspects of medical interventions are becoming more important. Cost effectiveness and the rational use of medicines are vital for the success of health care delivery systems (Walters & Smart, 1993:820; Whitaker, 1998:9). The ultimate objective of pharmaco-economics is to assist informed clinical decisions (Davey *et al.*, 1997:394).

Pharmaco-economic data are considered important in formulary decision making, but the reported usage of this data were relatively low (Clouse, 2002:S511; Walkom *et al.*, 2006:384).

The introduction of pharmaco-economics or cost effectiveness of medicines, in South Africa is inevitable, offering as it does a mean of assessing the cost benefits of pharmaceutical products (Jones, 2006:96).

In this chapter the concepts of managed health care, pharmaco-economics and drug utilisation, with special reference to acid reducing medicine were discussed. Examples of pharmaco-economic studies as related to acid-related disorders were provided to conceptualise the implementation of these tools as an aid for decision making in health care management.

CHAPTER 4:

EMPIRICAL INVESTIGATION

4.1 INTRODUCTION

In this chapter the research objectives, empirical research methodology and data analysis are discussed.

4.2 RESEARCH OBJECTIVES

The research objectives were divided into general and specific objectives.

4.2.1 GENERAL OBJECTIVE

The general objective of this study was to review the prescribing patterns and cost of acid reducing medicine according to a medicine claims database for the period from 2001 to 2006 in a section of the South African private health care market.

4.2.2 SPECIFIC OBJECTIVE

The specific objectives of the literature included the following:

- To investigate acid-related disorders and their treatment.
- To conceptualise what managed health care, pharmaco-economics and drug utilization entail, with special reference to acid reducing medicine.

The specific objectives of the empirical study included the following:

- To investigate the possible differences in the utilisation patterns and/or cost of medicine in general, before and after the implementation of the pricing regulations in May 2004.
- To investigate the prevalence and prescribing patterns of medicine items in general, as well as the costs associated with these medicine items.
- To investigate the prevalence and prescribing patterns of gastro-intestinal (GI) medicine items, as well as the costs associated with these medicine items.

- To analyse the prescription patterns of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.
- To analyse the prescribing patterns for different types (sub-pharmacological groups) of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.
- To determine the prevalence of acid reducing medicine items according to trade name and active ingredients.
- To analyse the prescribing patterns for individual acid reducing medicine items in South Africa, as well as the costs associated with these medicine items.
- To determine the influence of generic substitution on the cost and prescribing patterns of acid reducing medicine.
- To determine the prevalence and cost of combinations (PPIs prescribed together with amoxicillin, bismuth, clarithromycin, metronidazole and tetracycline on one prescription) used in the treatment of *H.pylori*.
- To determine the prescribed daily dose for acid reducing medicine with special reference to H₂RAs and PPIs according to active ingredient, strength and innovator or generic medicine item.

4.3 RESEARCH METHOD

A retrospective drug utilisation study was done on data provided by Interpharm Data systems® (Pty) Ltd. For the definition of a retrospective drug utilisation refer to section 3.3.2. No experiments, e.g. clinical trials, were done, therefore, the research design can be described as a non-experimental, retrospective, quantitative (refer to section 3.3.2) research.

The basic steps for conducting a drug utilisation study were described in chapter 3 (refer to figure 3.3). For the purpose of this study only the following steps will be included in the empirical investigation:

- The selection of the study population (see section 4.4)
- The selection of measuring instruments (see section 4.6)
- Data analysis (see section 4.7 and Chapter 5)

- The report and discussion of the results of the empirical investigation (see Chapter 5)
- Conclusions and recommendations based on the results of the empirical investigation (see Chapter 6)

4.4 STUDY POPULATION

Jaisingh (2000:5) defines a population as all the elements that are being studied. The total population consisted of all the prescriptions on the database for 2001, 2002, 2004, 2005 and 2006. The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for the whole 2003 and thus the prescribing patterns and costs of drugs associated with this period cannot be compared with the other periods. The study population consisted of all the prescriptions of patients using acid reducing medicine during 2001, 2002, 2004, 2005 and 2006.

The different strata were collected by following certain steps:

- All the prescriptions on the database were examined.
- All prescriptions containing acid reducing medicine were selected from the database.
- Acid reducing medicines were classified according to the MIMS classification system (Snyman, 2005:13a).
- Acid reducing medicines were classified according to pharmacological active ingredient.
- Acid reducing medicines were classified according to innovator or generic medicine items and dosages prescribed.

4.5 CLASSIFICATION SYSTEMS USED

The classification systems used in this study included: nappi code, MIMS and SAMF classification as well as the classification according to active ingredient and innovator/generic.

4.5.1 NAPPI CODE

The National Pharmaceutical Pricing Index (NAPPI) codes are widely used in the private health care industry (Medicover, 2007). A nappi code is a unique 9 digit long product code (Snyman, 2005:7a). A nappi code is an exclusive identifier for a given product which enables electronic

transfers throughout the health care delivery chain (Medikredit, 2007). The nappi codes provide information on the product name, pack size, strength and manufacturer.

4.5.2 MIMS CLASSIFICATION SYSTEM

The MIMS (Monthly Index of Medical Specialties) classification system classifies medicine according to its pharmacological action. The MIMS classifies acid reducers as antacids, antacids and combinations, H₂RAs, PPIs, cytoprotective agents and other acid reducers (Snyman, 2005:11a). There are currently no products listed as “other acid reducers”. For the purpose of this study antacids and antacids and combinations will be discussed as one category.

4.5.3 SAMF CLASSIFICATION SYSTEM

The SAMF (South African Medicines Formulary) classifies medicine according to its pharmacological active ingredient. The MIMS and SAMF were used to obtain the brand and generic name of the different acid reducing medicines.

4.6 MEASURING INSTRUMENTS

For the purpose of this study prevalence, frequency, cost, cost prevalence index and effect size (d-value) were used as measuring instruments.

4.6.1 PREVALENCE

Prevalence is a measure of the number of people in a population who have a particular disease at a given point in time (Everitt, 1998:260).

$\text{Prevalence} = \frac{\text{Number of cases of disease at a particular moment in time}}{\text{Size of the population (number of prescriptions) at that moment}}$

For the purpose of this study the prevalence will indicate the number of times a particular medicine item occurred in a time period of one year.

In this study the prevalence of the following medicine items was analysed as follows:

- The prevalence of all medicine items of the total database claimed during the study period.
- The prevalence of gastro-intestinal tract medicine items claimed during the study period.
- The prevalence of pharmacological group, e.g. acid reducing medicine items claimed during the study period.
- The prevalence of sub-pharmacological group, e.g. antacids, H₂RAs, PPIs and cytoprotective agents claimed during the study period.
- The prevalence of individual acid reducing medicine items e.g. Nexiam® 40mg, Adco-cimetidine® 400mg etc. that contain different active ingredients e.g. esomeprazole, cimetidine etc. claimed during the study period.
- The prevalence of acid reducing medicine items according to active ingredient, as claimed during the study years.
- The prevalence of innovator and generic medicine items claimed on the total database during the study periods.
- The prevalence of innovator and generic gastro-intestinal medicine items claimed during the study years.
- The prevalence of innovator and generic acid reducing medicine items claimed during the study period.
- The prevalence of innovator and generic medicine items according to the sub-pharmacological group, e.g. antacids, H₂RAs, PPIs and cytoprotective agents claimed during the study period.
- The prevalence of combination therapy (PPIs prescribed together with amoxicillin, bismuth, clarithromycin, metronidazole and tetracycline on one prescription) used in the treatment of *H.pylori*.

4.6.2 FREQUENCY

Frequency refers to the number of times that a particular value or category occurs in a set of data (Martin & Pierce, 1994:13). For the purpose of this study the terms prevalence and frequency are viewed as synonyms.

4.6.3 COST

Cost is the total value of all the resources that are consumed in the productions of a product or service (Struwig, 2001:58). With regard to this study cost is defined as expenses incurred in the provision of health care products such as medicine. The nature of cost has been thoroughly discussed in chapter 3.4.4. For the purpose of this study only the direct cost of the medication was included in the cost.

In this study the total medicine cost and the average cost per medicine item were analysed as follows:

- The total cost and average cost of all medicine items as well as the average cost per prescription on the total database claimed during the study period.
- The total cost and average cost of gastro-intestinal tract medicine items as well as the average cost per GIT prescription claimed during the study period.
- The total cost and average cost of pharmacological group, e.g. acid reducing medicine items as well as the average cost per prescription claimed during the study period.
- The total cost and average cost of sub-pharmacological group, e.g. antacids, H₂RAs, PPIs and cytoprotective agents claimed during the study period.
- The total cost and average cost of individual acid reducing medicine items e.g. Nexiam® 40mg, Adco-cimetidine® 400mg etc. that contain different active ingredients e.g. esomeprazole, cimetidine etc. claimed during the study period.
- The total cost and average cost of innovator and generic medicine items claimed on the total database during the study periods.
- The total cost and average cost of innovator and generic gastro-intestinal medicine items claimed during the study years.
- The total cost and average cost of innovator and generic acid reducing medicine items claimed during the study period.
- The total cost and average cost of innovator and generic medicine items according to active ingredient.

4.6.4 COST-PREVALENCE INDEX

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

$$\text{Cost prevalence index (CPI)} = \frac{\text{Cost \%}}{\text{Prevalence \%}}$$

The cost-prevalence index is an indicator of the expensiveness of acid reducing medicine and can be analysed as follows:

- If $\text{CPI} < 1$ then the therapy is relatively inexpensive.
- If $\text{CPI} = 1$ then there is equilibrium between the cost and prevalence of the therapy.
- If $\text{CPI} > 1$ then the therapy is relatively expensive.

In this study the CPI per medicine item was analysed as follows:

- The CPI of the top 20 acid reducers during the study period.
- The CPI of individual acid reducing medicine items e.g. Nexiam[®] 40mg, Adco-cimetidine[®] 400mg etc. that contain different active ingredients e.g. esomeprazole, cimetidine etc. claimed during the study period.

4.7 DATA ANALYSIS

The data were analysed by means of SAS 9.1[®] (SAS for Windows, 9.1, 2006).

4.7.1 DATA SOURCE

The data for this study were obtained from Interpharm Data systems[®] (Pty) Ltd. Data ranging from 1 January 2001 to 31 December 2001, 1 January 2002 to 31 December 2002, 1 January 2004 to 31 December 2004, 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006 were extracted from the database.

4.7.2 DATABASE

The database consists of all the prescriptions claimed through Interpharm Data systems® for the periods mentioned in section 4.4. The following fields were used in this study:

- Medical schemes codes, medical scheme member number and medical scheme dependent number
- The nappi code of the medicine product
- The description (trade name) of the drug
- The quantity of the drug that were dispensed
- The price of the drug
- The prescription number
- The date of dispensing
- Indicator for innovator or generic product

4.7.3 STATISTICAL ANALYSIS

For the purpose of the empirical investigation, various statistical methods were applied to analyse data as follows:

4.7.3.1 ARITHMETIC MEAN (AVERAGE)

The average value is usually represented by the arithmetic mean. This is simply the sum of the values divided by the number of values (Kirkwood, 1988:12).

$$\text{Mean} = \frac{\sum x}{n}$$

The Greek capital letter Σ (sigma) is used to represent *the sum of*, x denotes the values of the variables and n is the number of observations.

4.7.3.2 PERCENTAGE

A percentage can be defined as a fraction or a ratio with 100 understood as the denominator (a proportion multiplied by 1000). For example 0.98 equals a percentage of 98 (The free dictionary, 2007).

4.7.3.3 STANDARD DEVIATION

The standard deviation is one of the most common and useful measures of variability.

The standard deviation provides information about how the data vary about the mean. If the data are clustered around the mean, then the standard deviation will be small. The standard deviation will be large if the data are widely scattered about the mean (Jaisingh, 2000:47).

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

Where:

- $s \rightarrow$ standard deviation
- $x \rightarrow$ any value in the data set
—
- $\bar{x} \rightarrow$ arithmetic mean (average)
- $n \rightarrow$ number of observations.

4.7.3.4 D-VALUES/ EFFECT SIZES

According to Talheimer and Cook (2002:3) an effect size is the difference between two means divided by the standard deviation.

$$d = \frac{X_t - X_c}{S_{\max}}$$

Where:

- $d \rightarrow$ Cohen's d effect size
- $x_t \rightarrow$ average cost of treatment (mean)
- $x_c \rightarrow$ average cost of comparing treatment (mean)
- $S_{\max} \rightarrow$ maximum standard deviation.

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

- $d = 0.2 \rightarrow$ small effect with no practical significant difference.
- $d = 0.5 \rightarrow$ medium effect, which is observable and may be significant.
- $d = 0.8 \rightarrow$ large effect, which is significant and of practical importance.

For the purpose of this study the effect size (d -value) was used as a measuring tool, to determine whether the difference between the average costs of two comparing treatments was of practical significance. The d -values (effect sizes) were calculated for each year in reference to year 2001 (base year). The d -values (effect size) of 2005 and 2006 were also calculated in reference to 2004 to establish the influence of the single exit pricing regulations.

4.7.3.5 MEDIAN

The median of a set of observations is the value that falls in the middle (50%) when the observations are arranged in order of magnitude (Keller & Warrack, 2000:93). For example if there are n observations arranged in order of magnitude, then the median will be the middle value (if n is an odd number) or the mean (refer to section 4.7.3.1) of the two middle values (if n is an even number).

4.8 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENTS

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

Research was conducted from the viewpoint that all data obtained from the database were correct and accurate. This was a limitation of the study and will be listed in Chapter 6.3.

4.9 RESULTS AND DISCUSSION

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

4.10 CONCLUSION AND RECOMMENDATIONS

The conclusion and recommendations based on the results of the literature review and the empirical investigation will be discussed in Chapter 6.

4.11 ETHICAL ASPECTS

Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the medical scheme administrator providing the data to ensure confidentiality. Thus no specific patient, medical practice, pharmacy or medical scheme could be identified. Thus confidentiality of information was maintained throughout the study.

The data used in this study were analysed with permission from the Pharmacy Benefit Management (PBM) Company, utilising Interpharm Data systems (Pty.) Ltd. database.

4.12 SUMMARY

In this chapter the empirical investigation was discussed. The research objectives, research method, study population, measuring instruments and data analysis were described.

CHAPTER 5:

RESULTS AND DISCUSSION

5.1 INTRODUCTION

In this chapter the results of the empirical investigation will be reported and discussed. The results were for the following periods: 1 January 2001 to 31 December 2001; 1 January 2002 to 31 December 2002; 1 January 2004 to 31 December 2004; 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006.

According to a study conducted by Farmer (2001:208) who used a medicine claims database, Interpharm Data systems® in South Africa, the cost of proton pump inhibitors (R17 426 608. 51) represented 12.4% of the total cost of all prescriptions (46 645 prescriptions) issued during the study period (July 1999 to June 2000). In this dissertation comparisons will be made with this study where applicable.

For the purpose of this study, the total database was analysed and the gastro-intestinal tract (GIT) medicine items have been referred to as medicine items of the main pharmacological group (pharmacological group 12 according to the MIMS® classification system) (Snyman, 2007:12a). The acid reducing medicine items have been referred to as medicine items of the pharmacological group (group 12.4 according to the MIMS® classification system) and have been divided into six categories/sub-pharmacological groups namely: the antacids (group 12.4.1), antacids and combinations (group 12.4.2), histamine-2 receptor antagonists (H₂RAs) (group 12.4.3), proton pump inhibitors (PPIs) (group 12.4.4), cytoprotective agents (group 12.4.5) and other acid reducers (Snyman, 2007:230).

Due to the nature and extent of this study, the focus of the study was on acid reducing medicine. The literature study has proved both histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) effective for the treatment of acid-related disorders (refer to the following sections: 2.5.1.5, 2.5.2.6, 2.5.3.7 and 2.5.4.6). Therefore the focus for this study was particularly on H₂RAs and PPIs.

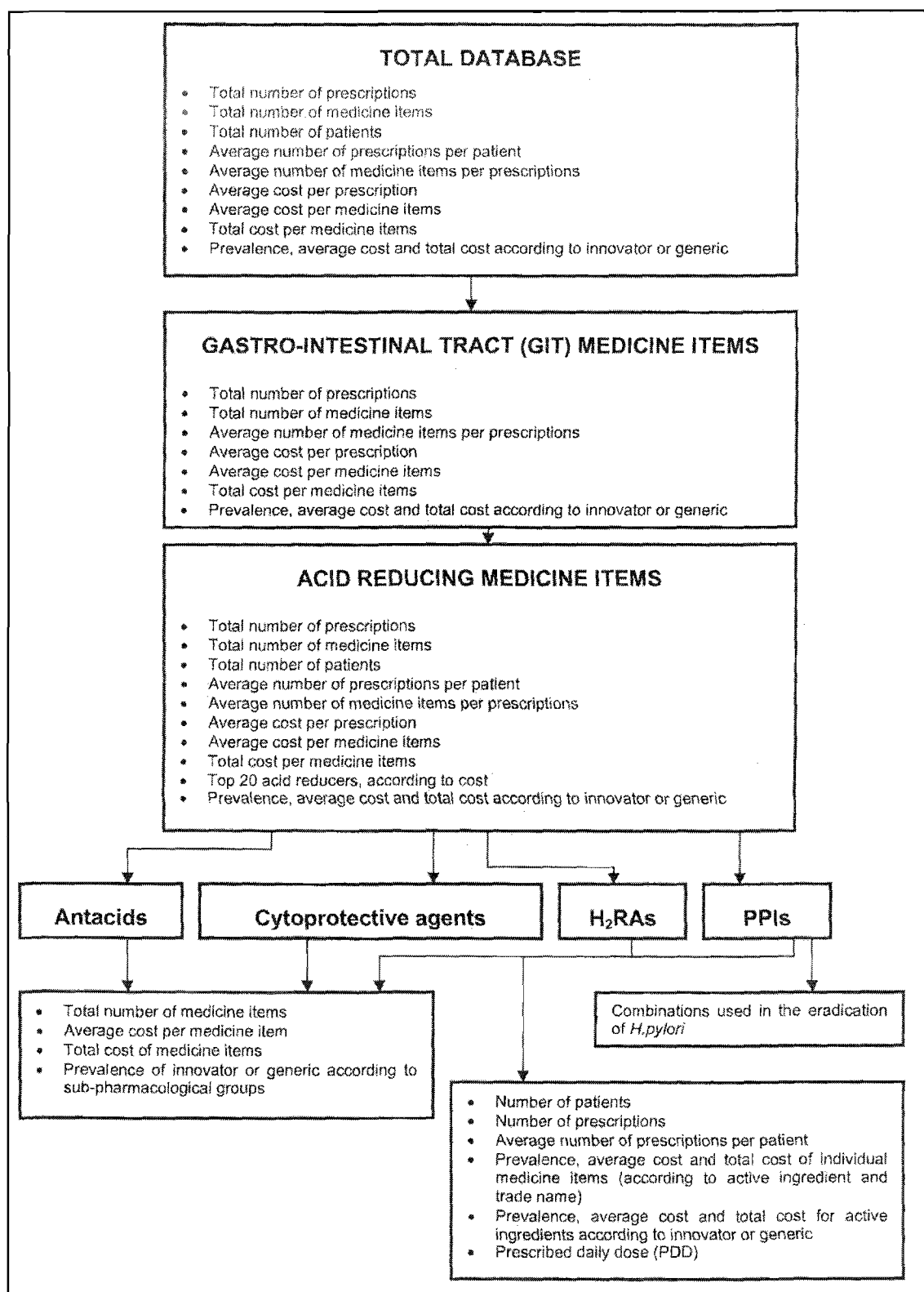


Figure 5.1: Schematic classification system of database.

5.2 TERMS AND DEFINITIONS

For the purpose of this study the following terms need to be explained.

5.2.1 ACTIVE INGREDIENT

An active ingredient is any component of a medicine item intended to provide a pharmacological activity or other direct effect in the diagnosis, treatment, alleviation or prevention of disease, or to affect the structure or any function of the body of humans or other animals. Active ingredients include those components of the medicine item that may undergo chemical change during the manufacture of the medicine item and be present in the medicine item in a modified form intended to give the specified activity or effect (CDER, 2007b).

5.2.2 MEDICINE ITEM

Medicine is a substance or mixture of substances which is accepted as being ethical by medical science and which is registered with the South African Medicines Control Council, to be administered or applied for the prevention, treatment or healing of an illness (Medihelp, 2007). For the purpose of this study the terms drug, medicine and medicine item all refer to a medicine item.

5.2.3 ACID REDUCING MEDICINE

Acid reducing medicine is medicine that is used in the management of acid-related disorders and classified in the pharmacological group 12.4 according to the MIMS® classification system. As previously mentioned, the acid reducing medicine items have been referred to as medicine items of the pharmacological group (group 12.4 according to the MIMS® classification system) and have been divided into six categories/sub-pharmacological groups namely: the antacids, histamine-2 H₂RAs, PPI and cytoprotective agents (Snyman, 2007:230). For the purpose of this study the following disorders are described as acid-related disorders: dyspepsia, peptic ulcer disease, gastro-oesophageal reflux disease and Zollinger-Ellison syndrome (refer to chapter 2).

5.2.4 INNOVATOR MEDICINE ITEMS

Innovator medicine items refer to medicines that are registered in South Africa, and that are currently protected by a patent or had been protected by a patent previously. Such medicines may be marketed either by the original patent holder or another entity (Pillay, 2006:1).

5.2.5 GENERIC MEDICINE ITEM

A generic medicine item is a medicine which is equivalent to a brand name (innovator) medicine. These drugs are usually, but not always, sold at a lower price than the innovator medicine items. Generic medicine items must contain the same active ingredient at the same strength as the innovator medicine items, and are required to meet the same pharmacological requirements for the preparation. Generics are therefore assumed to be identical in dose, strength, route of administration, safety, efficacy and intended use (Rognehaugh, 1998:91).

5.2.6 PRESCRIPTION

A prescription is a written instruction, by a prescriber accredited by law, for the preparation and administration of a medicine item or other treatment.

5.2.7 PATIENT

A patient is any person who receives medical attention, care or treatment. The person is most often ill or injured and in need of treatment by a physician or other medical professional. Health consumers or clients are other names for patient, usually used by insurance companies.

5.3 COMMENTS OF INTEREST WITH INTERPRETATION OF THE RESULTS

- The data of 2003 have been left out of the study due to the unavailability of the data in electronic format for this period and thus the usage and cost of drugs associated with this period cannot be compared with other periods. This was one of the limitations of this study (refer to section 6.3).
- The values of the data that were used have been rounded to two decimals and may not add up to 100 per cent.
- For the purpose of this study both antacids, and antacids and combinations were categorised in one group (Snyman, 2007:12a).
- For the purpose of this study the d-values (effect sizes) (see section 4.7.3.4) were calculated for each year in reference to year 2001 (base year). The d-values (effect size) of 2005 and 2006 were also calculated in reference to 2004 to establish the influence of the single exit pricing regulations (refer to section 3.5.3).
- Only $d \geq 0.8$ (practically significant difference) was used as this value indicated that the effect is large and of practical importance (refer to section 4.7.3.4).

5.4 OVERVIEW OF MEDICINE ITEMS ON THE TOTAL DATABASE

Table 5.1 provides the prescribing patterns of the total database, GIT and acid reducers for the five study years, 1 January 2001 to 31 December 2001; 1 January 2002 to 31 December 2002; 1 January 2004 to 31 December 2004; 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006.

Table 5.1: Results of the general prescribing patterns for the years 2001, 2002, 2004, 2005 and 2006.

Year	Description	Total database	GIT medicine	Acid reducers
2001	Number of prescriptions (N)	1 475 380	145 626	72 269
	Total number of medicine items prescribed (N)	2 951 326	179 556	80 773
	Average number of medicine items per prescription	2.00 ± 1.17	1.23 ± 0.49	1.12 ± 0.33
	Minimum number of medicine items per prescription	1.00	1.00	1.00
	Maximum number of medicine items per prescription	17.00	5.00	3.00
	Average cost per prescription in Rand (R) value	257.63 ± 271.06	193.38 ± 212.00	257.11 ± 184.58
	Total cost of medicine items in Rand (R) value	379 708 489.00	28 161 679.09	18 580 851.94
	Average cost per medicine item in Rand (R) value	128.66 ± 151.96	156.84 ± 183.75	230.04 ± 176.29
2002	Number of prescriptions (N)	2 076 236	190 667	97 712
	Total number of medicine items prescribed (N)	4 042 145	229 093	107 637
	Average number of medicine items per prescription	1.95 ± 1.17	1.20 ± 0.46	1.10 ± 0.31
	Minimum number of medicine items per prescription	1.00	1.00	1.00
	Maximum number of medicine items per prescription	23.00	6.00	4.00
	Average cost per prescription in Rand (R) value	289.63 ± 351.05	206.50 ± 213.73	268.47 ± 192.20
	Total cost of medicine items in Rand (R) value	601 350 325.00	39 372 936.30	26 232 978.81
	Average cost per medicine item in Rand (R) value	148.77 ± 205.25	171.86 ± 189.40	243.72 ± 184.18
2004	Number of prescriptions (N)	2 595 254	244 072	123 137
	Total number of medicine items prescribed (N)	5 305 846	295 738	135 401
	Average number of medicine items per prescription	2.04 ± 1.27	1.21 ± 0.48	1.10 ± 0.31
	Minimum number of medicine items per prescription	1.00	1.00	1.00
	Maximum number of medicine items per prescription	18.00	7.00	4.00
	Average cost per prescription in Rand (R) value	254.78 ± 397.84	181.28 ± 407.66	226.72 ± 187.10
	Total cost of medicine items in Rand (R) value	661 221 000.00	44 245 960.02	27 918 204.80
	Average cost per medicine item in Rand (R) value	124.62 ± 228.55	149.61 ± 362.05	206.19 ± 179.42

Table 5.1 (Continued): Results of the general prescribing patterns for the years 2001, 2002, 2004, 2005 and 2006.

Year	Description	Total database	GIT medicine	Acid reducers
2005	Number of prescriptions (N)	1 621 739	166 555	83 708
	Total number of medicine items prescribed (N)	3 606 992	207 557	92 565
	Average number of medicine items per prescription	2.22 ± 1.37	1.25 ± 0.52	1.11 ± 0.32
	Minimum number of medicine items per prescription	1.00	1.00	1.00
	Maximum number of medicine items per prescription	19.00	6.00	4.00
	Average cost per prescription in Rand (R) value	250.24 ± 403.60	164.42 ± 244.04	201.83 ± 182.99
	Total cost of medicine items in Rand (R) value	405 829 097.00	27 384 777.20	16 894 773.25
	Average cost per medicine item in Rand (R) value	112.51 ± 226.99	131.94 ± 204.01	182.52 ± 172.36
2006	Number of prescriptions (N)	996 787	108 802	52 842
	Total number of medicine items prescribed (N)	2 370 569	138 458	59 157
	Average number of medicine items per prescription	2.38 ± 1.44	1.27 ± 0.54	1.12 ± 0.34
	Minimum number of medicine items per prescription	1.00	1.00	1.00
	Maximum number of medicine items per prescription	18.00	6.00	4.00
	Average cost per prescription in Rand (R) value	280.06 ± 434.37	158.87 ± 180.76	196.69 ± 186.11
	Total cost of medicine items in Rand (R) value	279 160 657.60	17 300 562.83	10 393 732.16
	Average cost per medicine item in Rand (R) value	117.76 ± 237.81	124.23 ± 152.05	175.73 ± 172.55

The total number of prescriptions

The total number of prescriptions claimed increased from 2001 to 2004 and then decreased from 2004 to 2006 (refer to table 5.1). The same trend was observed with the number of prescriptions containing at least one GIT and an acid reducing medicine item (refer to table 5.1).

The total number of acid reducing prescriptions increased with 70.39% (n = 50 868) from 2001 to 2004 and decreased by 57.09% (n = 70 295) from 2004 to 2006 (refer to table 5.1).

A possible explanation for the accrument between 2001 and 2004 could be a rise in the number of medical schemes, medical scheme members and dependants administered by Interpharm Data systems® (Pty) Ltd. In turn the diminution from 2004 to 2006 may be explained by a decrease in the number of medical schemes; medical scheme members and dependants. The number of medical schemes administered by Interpharm Data systems® (Pty) Ltd. decreased from 80 in 2004 to 68 in 2005 and 35 in 2006.

Table 5.1.1 provides the percentage GIT and acid reducers' prescriptions represented as part of the total number of prescriptions for the five study years.

Table 5.1.1: Percentage GIT and acid reducers' prescriptions represented as part of the total number of prescriptions for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database	GIT	Acid reducers
2001	N = 1 475 380	9.87% (n = 145 626)	4.90% (n = 72 269)
2002	N = 2 076 236	9.18% (n = 190 667)	4.71% (n = 97 712)
2004	N = 2 595 254	9.40% (n = 244 072)	4.74% (n = 123 137)
2005	N = 1 621 739	10.27% (n = 166 555)	5.16% (n = 83 708)
2006	N = 996 787	10.92% (n = 108 802)	5.30% (n = 52 842)

% - The total number of GIT or acid reducer prescriptions claimed (n) for the specific period (year) divided by the total number of prescriptions (N) claimed during the corresponding year multiplied by hundred.

Although the number of GIT and acid reducers' prescriptions decreased from 2004 to 2006 there was still an increase in the percentage contribution made by both GIT and acid reducers' prescription to the prescriptions on the total database. There was a small decrease in percentage (< 1%) that GIT and acid reducers' prescriptions contributed to the total number of prescriptions on the database from 2001 to 2002. In turn there was a percentage increase in the contribution made to the total number of prescriptions containing either at least one GIT or acid reducing medicine item from 2002 to 2006 (refer to table 5.1.1).

The number of medicine items prescribed

The total number of medicine items prescribed increased from 2001 to 2004 and decreased from 2004 to 2006. The same pattern was observed with regard to GIT and acid reducing medicine items (refer to table 5.1.2).

The number of acid reducing medicine items increased with 67.63% (n = 54 628) from 2001 to 2004 and decreased 56.31% (n = 76 244) from 2004 to 2006 (refer to table 5.1.2).

As previously explained the increase and decrease during the study might be due to a rise in the number of medical schemes, medical scheme members and dependants administered by Interpharm Data systems® (Pty) Ltd. The number of medical schemes administered by Interpharm Data systems® (Pty) Ltd. decreased from 80 in 2004 to 68 in 2005 and 35 in 2006. Also the composition and change of medical schemes, members and dependants, as illustrated on the database(s) for the study periods, is only noted for possible influence on the medicine usage. In other words the "business side" and "risk management" fall outside the scope of this study, as this is from the viewpoint of this study uncontrollable.

Table 5.1.2 provides the percentage GIT and acid reducers' medicine items contributed with regard to the total number of medicine items for the five study years.

Table 5.1.2: Percentage contribution of GIT and acid reducing medicine items to the total number of medicine items for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database	GIT	Acid reducers
2001	N = 2 951 326	6.03% (n = 179 556)	2.74% (n = 80 773)
2002	N = 4 042 145	5.67% (n = 229 093)	2.66% (n = 107 637)
2004	N = 5 305 846	5.57% (n = 295 738)	2.55% (n = 135 401)
2005	N = 3 606 992	5.75% (n = 207 557)	2.57% (n = 92 565)
2006	N = 2 370 569	5.84% (n = 1 384 58)	2.50% (n = 59 157)

% - The total number of GIT or acid reducing medicine items claimed (n) for the specific period (year) divided by the total number of medicine items claimed (N) during the corresponding year multiplied by hundred.

Although the total number of medicine items decreased from 2004 to 2006, there was still a percentage increase in the contribution with the exception of acid reducing medicine items which decreased with 0.07% from 2005 to 2006. From 2001 to 2004 there was a decrease in percentage GIT and acid reducing medicine items that contributed to the total number of medicine items. From 2004 to 2006 there was an increase in the percentage contribution made by GIT medicine items to the total number of medicine items. There was also a percentage increase in the contribution made to the total number of medicine items by acid reducing medicine items from 2004 to 2005 but a percentage decrease was observed from 2005 to 2006 (refer to table 5.1.2). It seems that the usage of GIT and acid reducing medicine items does not have a linear function with regard to the total medicine usage for the study period.

The average cost per prescription

Table 5.1.3 provides the average cost per prescription of the total database, GIT and acid reducers for the five study years.

Table 5.1.3: The average cost per prescription of the total database, GIT and acid reducing medicine items represented for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database	GIT	Acid reducers
2001	R257.63±271.06	R193.38±212.00	R257.11±184.58
2002	R289.63±351.05	R206.50±213.73	R268.47±192.20
2004	R254.78±397.84	R181.28±407.66	R226.72±187.10
2005	R250.24±403.60	R164.42±244.04	R201.83±182.99
2006	R280.06±434.37	R158.87±180.76	R196.69±186.11

The average cost per prescription for the total database increased from 2001 to 2002, decreased from 2002 to 2005 and then increased again from 2005 to 2006 (refer to table 5.1.3).

The average cost per prescription for both the GIT and acid reducing medicine items increased from 2001 to 2002 and decreased from 2002 to 2006 (refer to table 5.1.3).

During 2001 the rand value of the average cost per prescription for acid reducers was similar to the average cost per prescription of all medicine items claimed through the database (table 5.1.3).

There was an increase of 8.71% ($n = R22.43$) in the average cost per prescription on the total database against a decrease of 17.85% ($n = R34.51$) in the average cost per GIT prescription and 23.50% ($n = R60.42$) in the average cost per acid reducers' prescription from 2001 to 2006. The decrease in the average cost per prescription might be the result of the implementation of the legislation of generic substitution (refer to section 3.5.1) and the new pricing regulations (refer to section 3.5.3).

Table 5.1.3.1 gives the effect size (d-value) as regarding the average cost per prescription between the relevant study years.

Table 5.1.3.1: The effect sizes calculated between the average cost per prescription of the total database, GIT and acid reducers for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database		GIT		Acid reducers	
	2001	2004	2001	2004	2001	2004
2001						
2002	0.09		0.06		0.06	
2004	0.01		0.02		0.20	
2005	0.02	0.01	0.11	0.04	0.30	0.13
2006	0.05	0.06	0.16	0.05	0.32	0.16

The d-values were of no practical significance, however, there was an increase in the case of acid reducers for the relevant years (refer to section 4.7.3.4).

The total cost of medicine items

The total cost of medicine items increased from 2001 to 2004 and decreased from 2004 to 2006. This trend was true for the total database, GIT and acid reducing medicine items (refer to table 5.1.4).

The total cost of acid reducing medicine items on the database increased with 50.25% ($n = R9\ 337\ 352.86$) from 2001 to 2004. However, the total cost of acid reducing medicine items decreased with 62.77% ($n = R17\ 524\ 472.64$) from 2005 to 2006 (table 5.1.4).

The total volume (prevalence) of medicine items and the unit price (average cost) influence the total cost of medicine items. Therefore the decrease from 2004 to 2006 might be explained by the decrease in the number of prescriptions (see table 5.1.1) and medicine items (table 5.1.2) prescribed on the database together with the decrease in the average cost.

Table 5.1.4 provides the percentage that GIT and acid reducing medicine items represented as part of the total cost of all medicine items claimed for the five study years.

Table 5.1.4: Percentage contribution of GIT and acid reducing medicine items to the total cost of medicine items for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database	GIT	Acid reducers
2001	N = R379 708 489.00	7.42% (n = R28 161 679.09)	4.89% (n = R18 580 851.94)
2002	N = R601 350 325.00	6.55% (n = R39 372 936.30)	4.36% (n = R26 232 978.81)
2004	N = R661 221 000.00	6.69% (n = R44 245 960.02)	4.22% (n = R27 918 204.80)
2005	N = R405 829 097.00	6.75% (n = R27 384 777.20)	4.16% (n = R16 894 773.25)
2006	N = R279 160 657.60	6.20% (n = R17 300 562.83)	3.72% (n = R10 393 732.16)

% - The cost of GIT or acid reducing medicine items claimed (n) for the specific period (year) divided by the total cost of all the medicine items claimed (N) for the corresponding year multiplied by hundred.

Table 5.1.4 shows that the total cost of all the medicine items claimed as well as the total cost of GIT and acid reducing medicine items increased from 2001 to 2004. While the total cost of all medicine items claimed as well as the total cost of GIT and acid reducing medicine items decreased from 2004 to 2006. As previously explained the increase and decrease during the study might be due to a rise in the number of medical schemes, medical scheme members and dependants administered by Interpharm Data systems® (Pty) Ltd. The number of medical schemes administered by Interpharm Data systems® (Pty) Ltd. decreased from 80 in 2004 to 68 in 2005 and 35 in 2006.

The percentage cost that GIT medicine items represented as part of the total cost decreased from 2001 to 2002, increased from 2002 to 2005 and then decreased from 2005 to 2006 (table 5.1.4). While table 5.1.2 shows that the percentage that GIT medicine items contributed to the total number of medicine items claimed decreased from 2001 to 2004 and then increased from 2004 to 2006.

The percentage cost that acid reducers contributed to the total cost decreased continuously from 2001 to 2006 (table 5.1.4). While table 5.1.2 shows that the percentage that acid reducers contributed to the total number of medicine items claimed decreased from 2001 to 2004, increased from 2004 to 2005 and then decreased again from 2005 to 2006.

The decrease in the percentage cost contribution of GIT and acid reducing medicine items, from 2004 to 2006, might be the result of the implementation of the legislation of generic substitution (refer to section 3.5.1) and the new pricing regulations (refer to section 3.5.3).

The average cost per medicine item

Table 5.1.5 provides the average cost per medicine items of the total database, GIT and acid reducing medicine items for the five study years.

Table 5.1.5: The average cost per medicine items of the total database, GIT and acid reducing medicine items represented for the years 2001, 2002, 2004, 2005 and 2006.

Year	Total database	GIT	Acid reducers
2001	R128.66±151.96	R156.84±183.75	R230.04±176.29
2002	R148.77±205.25	R171.86±189.40	R243.72±184.18
2004	R124.62±228.55	R149.61±362.05	R206.19±179.42
2005	R112.51±226.99	R131.94±204.01	R182.52±172.36
2006	R117.76±237.81	R124.23±152.05	R175.73±172.55

The average cost per medicine items decreased with 8.47% (n = R10.90), 20.51% (n = R32.61) and 23.61% (n = R54.31) respectively for the total database, GIT and acid reducing medicine items from 2001 to 2006 (refer to table 5.1.5).

The decrease in average cost per GIT and acid reducers' prescriptions were higher than the decrease in the average cost per GIT and acid reducing medicine item (refer to table 5.1.3 and table 5.1.5). The average cost per GIT and acid reducing medicine items was higher than the average cost per medicine item on the total database (table 5.1.5).

The reduction in the average cost per medicine item for GIT and acid reducers could possibly be explained by the introduction of the single exit price (SEP) (refer to section 3.5.3) and generic substitution (refer to section 3.5.1). Another explanation for this decrease might be that there was an increase in the percentage generic GIT and acid reducing medicine items claimed from 2001 to 2006 (refer to table 5.32). The average cost per medicine item on the total

database was lower than the average cost per GIT medicine item as well as the average cost per acid reducers. This may be the result of a wider range of medicine items and prices.

A possible explanation for the relative high average cost per acid reducing medicine item might be that acid reducers were relatively expensive medicine items. This will be further investigated later in this chapter (refer to section 5.5.3). The cost prevalence index (CPI) will be used as the relevant measuring instrument (refer to section 4.6.4).

Table 5.1.5.1 illustrates the effect size (d-value) calculated for the difference between the average cost per medicine item between the different study years, for medicine items on the total database, GIT and acid reducing medicine items.

Table 5.1.5.1: The effect sizes calculated between the average cost per medicine item of the total database, GIT and acid reducing medicine items, for the years 2001, 2002, 2004, 2005 and 2006.

	Total database		GIT		Acid reducers	
Year	2001	2004	2001	2004	2001	2004
2001						
2002	0.10		0.08		0.07	
2004	0.02		0.02		0.13	
2005	0.07	0.05	0.12	0.05	0.26	0.12
2006	0.05	0.03	0.17	0.07	0.31	0.17

The relevant effect size (d-values) were of no practical significant value (refer to section 4.7.3.4).

Summary

Both the prevalence and total cost of medicine items increased from both 2001 to 2002 and 2002 to 2004, while it decreased from 2004 to 2006. The average cost per prescription and the average cost per medicine item, however, increased from 2001 to 2002 and decreased from 2002 to 2004 and from 2004 to 2006. The decrease in the prevalence might be explained by a number of factors namely a change in the number and profile of the medical scheme claims, medical scheme members as well as changes in the treatment patterns of acid-related disorders. The reduction in the cost of medicine items could be the result of the implementation of the new pricing regulation within 2004 (refer to chapter 3; section 3.5.3) and an increased in the use of generic items (refer to section 3.5.1).

5.5 ANALYSIS OF ACID REDUCING MEDICINE ITEMS

5.5.1.1 OVERVIEW OF ACID REDUCING MEDICINE ITEMS ACCORDING TO SUB-PHARMACOLOGICAL GROUPS

In the following section an in depth study regarding the prevalence and average cost of acid reducing medicines will be done.

Table 5.2 gives an overview of the prevalence, average cost per medicine item and the total cost for the different sub-pharmacological groups of acid reducers for the five study years.

Table 5.2: An overview of the prevalence and cost of different sub-pharmacological groups of acid reducing medicine items for the years 2001, 2002, 2004, 2005 and 2006.

Year	Description	Antacids	H ₂ RAs	PPIs	Cytoprotective agents	Total acid reducers
2001	Total number of medicine items prescribed	24 674	12 606	39 730	3 763	80 773
	Total cost of medicine items in Rand (R) value	1 610 143.71	2 180 375.21	14 260 275.62	530 057.40	18 580 851.94
	Average cost per medicine item in Rand (R) value	65.26 ± 41.12	172.96 ± 110.28	358.93 ± 148.93	140.86 ± 93.63	230.04±176.29
2002	Total number of medicine items prescribed	32 560	16 147	54 369	4 561	107 637
	Total cost of medicine items in Rand (R) value	2 468 744.24	2 746 023.34	20 248 112.06	770 099.17	26 232 978.81
	Average cost per medicine item in Rand (R) value	75.83 ± 54.99	170.06 ± 117.63	372.42 ± 156.62	168.84 ± 118.38	243.72±184.18
2004	Total number of medicine items prescribed	38 409	20 861	71 279	4 852	135 401
	Total cost of medicine items in Rand (R) value	2 215 786.11	2 703 804.42	22 228 724.41	769 889.86	27 918 204.80
	Average cost per medicine item in Rand (R) value	57.69 ± 46.81	129.61 ± 149.93	331.86 ± 166.23	158.67 ± 110.98	206.19±179.42
2005	Total number of medicine items prescribed	25 066	15 257	48 658	3 584	92 565
	Total cost of medicine items in Rand (R) value	1 236 040.50	2 155 250.43	12 802 166.37	611 315.95	16 894 773.25
	Average cost per medicine item in Rand (R) value	52.92 ± 45.05	141.26 ± 183.78	263.11 ± 168.00	170.57 ± 114.39	182.52±172.36
2006	Total number of medicine items prescribed	15 879	10 800	30 517	1 961	59 157
	Total cost of medicine items in Rand (R) value	932 473.48	1 709 395.59	7 371 767.93	380 095.16	10 393 732.16
	Average cost per medicine item in Rand (R) value	58.72 ± 57.13	158.28 ± 183.17	241.56 ± 177.21	193.83 ± 128.96	175.73±172.55

H₂RA – Histamine-2 receptor antagonist

PPI – Proton pump inhibitor

The prevalence of acid reducing medicine items according to sub-pharmacological group

Table 5.2.1 provides an overview of the prevalence percentage of the different sub-pharmacological groups of the acid reducers for the five study years.

Table 5.2.1: Prevalence percentage of antacids, H₂RA, PPIs and cytoprotective items for 2001, 2002, 2004, 2005 and 2006.

Year	Total Acid reducers	Antacids	H ₂ RA	PPIs	Cytoprotective agents
2001		30.55%	15.61%	49.19%	4.66%
	N = 80 773	(n = 24 674)	(n = 12 606)	(n = 39 730)	(n = 3 763)
2002		30.25%	15.00%	50.51%	4.24%
	N = 107 637	(n = 32 560)	(n = 16 147)	(n = 54 369)	(n = 4 561)
2004		28.37%	15.41%	52.64%	3.58%
	N = 135 401	(n = 38 409)	(n = 20 861)	(n = 71 279)	(n = 4 852)
2005		27.08%	16.48%	52.57%	3.87%
	N = 92 565	(n = 25 066)	(n = 15 257)	(n = 48 658)	(n = 3 584)
2006		26.84%	18.26%	51.59%	3.31%
	N = 59 157	(n = 15 879)	(n = 10 800)	(n = 30 517)	(n = 1 961)

Prevalence % - The number of medicine items (n) claimed for the specific period (year) divided by the total number of medicine items (N) claimed for the corresponding year multiplied by hundred.

Table 5.2.1 further shows that the prevalence percentage of antacids and the cytoprotective agents decreased from 2001 to 2006, while the prevalence percentage of histamine-2 receptor antagonist (H₂RAs) decreased from 2001 to 2002 and increased from 2004 to 2006. The prevalence percentage of proton pump inhibitors (PPIs) increased from 2001 to 2004 and decreased from 2004 to 2006.

The prevalence percentage of antacids and the cytoprotective agents decreased respectively with 3.71% and 1.35% from 2001 to 2006. The prevalence percentage of H₂RAs and PPIs increased respectively with 2.65% and 2.40% from 2001 to 2006 (table 5.2.1).

The prevalence percentage of PPIs was constantly the highest between the different sub-pharmacological groups of acid reducing medicine over the study years and contributed to about half of all the acid reducers.

Total cost of acid reducing medicine items according to sub-pharmacological group

An overview of the percentage cost contribution of the different sub-pharmacological groups of the total cost of acid reducing medicines for the five study years is provided in table 5.2.2.

Table 5.2.2: Cost percentage of antacids, H₂RA, PPIs and cytoprotective agents for 2001, 2002, 2004, 2005 and 2006.

Year	Total acid reducers	Antacids	H₂RA	PPIs	Cytoprotective agents
2001		8.67%	11.73%	76.75%	2.85%
	N = R18 580 851.94	(n = R1 610 143.71)	(n = R2 180 375.21)	(n = R14 260 275.62)	(n = R530 057.40)
2002		9.41%	10.47%	77.86%	2.94%
	N = R26 232 978.81	(n = R2 468 744.24)	(n = R2 746 023.34)	(n = R20 248 112.06)	(n = R770 099.17)
2004		7.94%	9.68%	79.62%	2.76%
	N = R27 918 204.80	(n = R2 215 786.11)	(n = R2 703 804.42)	(n = R22 228 724.41)	(n = R769 889.86)
2005		7.36%	12.83%	76.18%	3.64%
	N = R16 894 773.25	(n = R1 236 040.50)	(n = R2 155 250.43)	(n = R12 802 166.37)	(n = R611 315.95)
2006		8.97%	16.85%	70.93%	3.66%
	N = R10 393 732.16	(n = R932 473.48)	(n = R1 709 395.59)	(n = R7 371 767.93)	(n = R380 095.15)

% - The cost of medicine items claimed (n) in a specific sub-pharmacological group for the specific period (year) divided by the total cost of all acid reducing medicine items (N) for the corresponding year multiplied by hundred.

Table 5.2.2 shows that the cost percentage of antacids, H₂RAs and the cytoprotective agents as part of the total cost of acid reducing medicine items increased with respectively 0.3%, 5.12% and 0.78%, from 2001 to 2006. While the cost percentage of PPIs decreased with 5.82% from 2001 to 2006.

The percentage cost of H₂RAs contributed to the total cost decreased from 2001 to 2004 and increased from 2004 to 2006. However, there was an increase of 5.12% in the percentage cost H₂RAs represented of the total cost of acid reducers from 2001 to 2006 (table 5.2.2). There might be a number of explanations for this trend. The first explanation includes that the new pricing legislation (refer to section 3.5.3) caused a drop in the average cost per medicine item. This might have led to a small price difference between generic and innovator medicine items. The consumer might rather have preferred the innovator medicine item with slightly higher price. However, limitations by the third party payers' referred prices or co-payments could eliminate the patients' preferred choice. The second explanation might be that the patient was not being informed about generic substitution, resulting in the patient's buying of the more expensive innovator medicine item. A third possible explanation might be the relative high prevalence of Zantac® effervescent tablets (150 mg and 300mg) during the five study years (refer to section 5.5.3). Zantac® effervescent tablets (150 mg and 300mg) were among the top five H₂RAs, according to cost, for the five study years (refer to table 5.19).

Table 5.2.2 shows that the cost percentage of PPIs increased from 2001 to 2004 and then decreased from 2004 to 2006. There was a decrease of 5.82% in the cost percentage of PPIs contributed to the total cost of acid reducers from 2001 to 2006. A possible explanation for this trend might be a combination of generic substitution (refer to section 3.5.1) and the influence of the new pricing legislation (refer to section 3.5.3).

The PPIs contributed continuously to more than 70% of the total cost of all acid reducing medicine items during the five study years (table 5.2.2).

The average cost per medicine item of acid reducers according to sub-pharmacological group

Table 5.2.3 reviews an overview of the average cost of the different sub-pharmacological groups of the acid reducers for the five study years.

Table 5.2.3: Average cost per antacids, H₂RAs, PPIs and cytoprotective agents for 2001, 2002, 2004, 2005 and 2006.

Year	Antacids	H ₂ RA	PPIs	Cytoprotective agents
2001	n = R65.26±41.12	n = R172.96±110.28	n = R358.93±148.93	n = R140.86±93.63
2002	n = R75.83±54.99	n = R170.06±117.63	n = R372.42±156.62	n = R168.84±118.38
2004	n = R57.69±46.81	n = R129.61±149.93	n = R331.86±166.23	n = R158.67±110.98
2005	n = R52.92±45.05	n = R141.26±183.78	n = R263.11±168.00	n = R170.57±114.39
2006	n = R58.72±57.13	n = R158.28±183.17	n = R241.56±177.21	n = R193.83±128.96

Table 5.2.3 shows that the average cost per medicine item for antacids increased from 2001 to 2002; decreased from 2002 to 2005 and increased from 2005 to 2006. The average cost per antacids was the lowest during 2005 and the highest during 2002.

The average cost per H₂RA medicine item decreased from 2001 to 2004 and increased from 2004 to 2006. The average cost per H₂RA medicine items was the highest during 2002 and the lowest during 2004 (see table 5.2.3).

The average cost per PPI medicine item increased from 2001 to 2002 and decreased from 2002 to 2006. The average cost per PPI medicine item was the highest during 2002 and the lowest during 2006 (see table 5.2.3).

The average cost per cytoprotective agent increased from 2001 to 2002, decreased from 2002 to 2004 and increased from 2004 to 2006. The average cost per cytoprotective agent was the lowest during 2001 and the highest during 2006 (see table 5.2.3).

The average cost per medicine item for antacids, H₂RAs and PPIs decreased respectively with 10.02%, 8.49% and 32.72%, from 2001 to 2006. The reduction in the average cost of medicine items could be the result of the implementation of the new pricing regulation within 2004 (refer to chapter 3; section 3.5.3) and an increase in both the usage and availability of generic items

(refer to section 3.5.1). The average cost per cytoprotective agent increased with 37.61% from 2001 to 2006 (table 5.2.3).

The average cost per for PPI medicine item was the highest of all acid reducing medicine items for the five study years (table 5.2.3).

5.5.1.2 AN OVERVIEW OF THE NUMBER OF PRESCRIPTIONS PER PATIENT

Table 5.3 gives an overview of the number of patients and the average number of prescriptions per patient for the five study years, 1 January 2001 to 31 December 2001; 1 January 2002 to 31 December 2002; 1 January 2004 to 31 December 2004; 1 January 2005 to 31 December 2005 and 1 January 2006 to 31 December 2006.

Table 5.3: An overview of the number of patients, average number of prescriptions per patient and total number of prescriptions for 2001, 2002, 2004, 2005 and 2006.

Year	Description	Total database	Acid Reducers	PPIs	H ₂ RA
2001	Number of patients	337 003	40 141	21 550	8 553
	Average number of prescriptions per patient	4.37±4.45	1.80±1.67	1.84±1.75	1.47±1.33
	Total number of prescriptions	1 475 380	72 269	39 621	12 590
2002	Number of patients	490 198	53 895	28 946	10 967
	Average number of prescriptions per patient	4.23±4.52	1.81±1.75	1.87±1.87	1.47±1.38
	Total number of prescriptions	2 076 236	97 712	54 221	16 124
2004	Number of patients	657 009	68 168	35 718	14 657
	Average number of prescriptions per patient	3.94±4.27	1.81±1.74	1.99±1.99	1.41±1.23
	Total number of prescriptions	2 595 254	123 137	71 049	20 787
2005	Number of patients	379 352	43 419	22 795	10 236
	Average number of prescriptions per patient	4.26±4.87	1.93±2.04	2.13±2.29	1.49±1.42
	Total number of prescriptions	1 621 739	83 708	48 515	15 213
2006	Number of patients	264 272	28 073	15 029	7 400
	Average number of prescriptions per patient	3.76±4.46	1.88±1.95	2.03±2.12	1.46±1.33
	Total number of prescriptions	996 787	52 842	30 442	10 768

The number of patients using acid reducers, H₂RAs and PPIs

Table 5.3.1 lists the number of patients using acid reducers, H₂RAs and PPIs for the five study years.

Table 5.3.1: The number of patients who received acid reducers, H₂RAs and PPIs for 2001, 2002, 2004, 2005 and 2006.

Year	Total number of patients on the database	The total number of patients who received acid reducers	The total number of patients who received PPIs	The total number of patients who received H ₂ RAs
2001	337 003	11.91%* N = 40 141	53.69% (n = 21 550)	21.31% (n = 8 553)
2002	490 198	10.99%* N = 53 895	53.71% (n = 28 946)	20.35% (n = 10 967)
2004	657 009	10.38%* N = 68 168	52.40% (n = 35 718)	21.50% (n = 14 657)
2005	379 352	11.45%* N = 43 419	52.50% (n = 22 795)	23.57% (n = 10 236)
2006	264 272	10.62%* N = 28 073	53.54% (n = 15 029)	26.36% (n = 7 400)

%* - The total number of patients, who received prescriptions containing acid reducing medicine, for the specific period (year) divided by the total number of patients on the database for the corresponding year multiplied by hundred.

% - The total number of patients, who received prescriptions containing H₂RA or PPI medicine items (n), for the specific period (year) divided by the total number of patients, who received prescriptions containing acid reducing medicine items (N) for the corresponding year multiplied by hundred.

Table 5.3.1 shows that the total number of patients increased from 2001 to 2004 and then decreased from 2004 to 2006. This trend was also observed with regard to patients using acid reducers, H₂RAs and PPIs. A possible explanation for the accrument between 2001 and 2004 could be a rise in the number of medical schemes, medical scheme members and dependants administered by Interpharm Data systems® (Pty) Ltd. In turn the decrease from 2004 to 2006 may be explained by a decrease in the number of medical schemes; medical scheme members and dependants that claimed through this medicine claims database. The number of medical schemes administered by Interpharm Data systems® (Pty) Ltd. decreased from 80 in 2004 to 68 in 2005 and 35 in 2006.

The percentage patients, who received prescriptions containing acid reducing medicine items decreased with 1.29% from 2001 to 2006. The percentage patients, who received prescriptions containing PPI medicine items, stayed reasonably constant during the five study years, while the percentage patients, who received prescriptions containing H₂RA medicine items, increased with 5.05% from 2001 to 2006 (table 5.3.1).

The total number of prescriptions

The total number of prescriptions (containing acid reducers, H₂RAs and PPIs) claimed during the five study years, are indicated in Table 5.3.2.

Table 5.3.2: The total number of prescriptions (containing acid reducers, H₂RAs and PPIs) claimed during 2001, 2002, 2004, 2005 and 2006.

Year	Total database	Acid Reducers	PPIs	H ₂ RAs
2001	1 475 380	N = 72 269	54.82% (n = 39 621)	17.42% (n = 12 590)
2002	2 076 236	N = 97 712	55.49% (n = 54 221)	16.50% (n = 16 124)
2004	2 595 254	N = 123 137	57.70% (n = 71 049)	16.88% (n = 20 787)
2005	379 352	N = 83 708	57.96% (n = 48 515)	18.71% (n = 15 213)
2006	996 787	N = 52 842	57.61% (n = 30 442)	20.38% (n = 10 768)

% - The number of prescriptions containing H₂RA or PPI medicine items (n), for the specific period (year) divided by the total number of prescriptions containing acid reducing medicine items (N) for the corresponding year multiplied by hundred.

Table 5.3.2 reveals that the percentage of prescriptions that contained PPIs and H₂RAs, increased respectively with 2.79% and 2.96%, from 2001 to 2006.

The average number of prescriptions per patient

Table 5.3.3 gives the average number of prescriptions (containing acid reducers, H₂RAs and PPIs) per patient for the five study years.

Table 5.3.3: The average number of prescriptions per patient (on the database as well as prescriptions containing acid reducers, H₂RAs and PPIs) for 2001, 2002, 2004, 2005 and 2006.

Year	Total database	Acid Reducers	PPIs	H ₂ RAs
2001	4.37±4.45	1.80±1.67	1.84±1.75	1.47±1.33
2002	4.23±4.52	1.81±1.75	1.87±1.87	1.47±1.38
2004	3.94±4.27	1.81±1.74	1.99±1.99	1.41±1.23
2005	4.26±4.87	1.93±2.04	2.13±2.29	1.49±1.42
2006	3.76±4.46	1.88±1.95	2.03±2.12	1.46±1.33

Table 5.3.3 shows that the average number of prescriptions per patient on the total database decreased from 2001 to 2004, increased from 2004 to 2005 and again decreased from 2005 to 2006. The average number of prescriptions (containing PPIs or acid reducers) per patient increased respectively with 19.00% and 4.44% from 2001 to 2006, while the number of prescriptions (containing H₂RA medicine items) per patient decreased with 0.68% from 2001 to 2006. Thus the number of prescriptions (containing H₂RA medicine items) per patient stayed reasonably constant during the study years. The average number of prescriptions per patient was the highest for prescriptions, containing acid reducers, PPIs and H₂RAs, during 2005.

Summary

Both the number of patients and the number of prescriptions increased from both 2001 to 2004, while it decreased from 2004 to 2006. A possible explanation for this increase between 2001 and 2004 could be a rise in the number of medical schemes, medical scheme members and dependants administered by Interpharm Data systems® (Pty) Ltd. during 2001 to 2004. In turn the decrease from 2004 to 2006 may be explained by a decrease in the number of medical schemes; medical scheme members and dependants. The number of medical schemes administered by Interpharm Data systems® (Pty) Ltd. decreased from 80 in 2004 to 68 in 2005 and 35 in 2006.

5.5.2 PREVALENCE OF ACID REDUCING MEDICINE

In the following section the prevalence of acid reducing medicine was discussed according to the active ingredient and trade name.

5.5.2.1 PREVALENCE OF ACID REDUCING MEDICINE ACCORDING TO TRADE NAME

The prevalence of acid reducing medicine was discussed according to trade name. The top 20 acid reducers for 2001, 2002, 2004, 2005 and 2006 were identified according to the cost.

The top 20 acid reducers for 2001

Table 5.4 provides the prevalence of the top 20 acid reducers according to cost for 2001, however the treatment period was not taken into consideration for calculation purposes.

Table 5.4: The prevalence of the top 20 acid reducers for 2001, according to cost.

Trade name	DF	Prevalence	Prevalence %	Cost (R)	Cost %	CPI
Lanzor® 30mg ^I	Cap	9 704	12.01	3 866 295.47	20.81	1.73
Losec mups® 20mg ^I	Tab	8 361	10.35	3 456 060.37	18.60	1.80
Lanzor® 15mg ^I	Cap	5 151	6.38	1 480 051.48	7.97	1.25
Pantoloc® 40mg ^I	Tab	3 384	4.19	1 324 728.59	7.13	1.70
Pariet® 20mg ^I	Tab	3 703	4.58	1 180 139.47	6.35	1.39
Losec mups® 10mg ^I	Tab	3 354	4.15	959 827.11	5.17	1.24
Controloc® 40mg ^I	Tab	2 133	2.64	793 267.95	4.27	1.62
Pariet® 10mg ^I	Tab	2 231	2.76	520 978.63	2.80	1.02
Gaviscon aniseed® ^I	Sus	7 014	8.68	421 516.34	2.27	0.26
Ulsanic® ^I	Sus	2 272	2.81	343 218.77	1.85	0.66
Gaviscon advance® ^I	Sus	1 971	2.44	270 669.40	1.46	0.60
Zantac® eff 150mg ^I	Tab	1 501	1.86	238 666.59	1.28	0.69
Lenamet® 400mg ^G	Tab	1 191	1.47	208 802.35	1.12	0.76
Mucaïne® ^I	Sus	2 941	3.64	196 775.63	1.06	0.29
Ranhexal® 150mg ^G	Tab	1 208	1.50	195 984.17	1.05	0.71
Losec mups® 40mg ^I	Tab	303	0.38	191 060.01	1.03	2.74
Adco-cimetidine® 400mg ^G	Tab	978	1.21	190 379.58	1.02	0.85
Losec® Triple pack ^I	Cap	266	0.33	180 572.15	0.97	2.95
Ulsec® 20mg ^G	Cap	518	0.64	518 061.25	2.79	4.35
Ranhexal® 300mg ^G	Tab	542	0.67	126 455.41	0.68	1.01

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Prevalence % - The number of the specific medicine item claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of the specific medicine items claimed for the specific period (year) divided by the total cost of the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.4 shows that Lanzor® 30mg was the acid reducer with the highest prevalence (n = 9704) and cost (n = R3 866 295.47) during 2001. The acid reducer with the highest cost prevalence index (CPI) during 2001 was Ulsec® 20mg (CPI = 4.35). Gaviscon aniseed® (antacid) was the acid reducer in the top 20 with the lowest CPI (CPI = 0.26). Twelve of the top 20 acid reducers have a CPI > 1 (refer to section 4.6.4) which includes eleven PPIs. This indicates that these twelve PPIs were relatively expensive.

The top 20 acid reducers for 2002

Table 5.5 provides the prevalence of the top 20 acid reducers according to cost for 2002, however the treatment period was not taken into consideration for calculation purposes.

Table 5.5: The prevalence of the top 20 acid reducers for 2002, according to cost.

Trade name	DF	Prevalence	Prevalence %	Cost (R)	Cost %	CPI
Lanzor® 30mg ^I	Cap	10 643	9.89	4 736 747.05	18.06	1.83
Losec mups® 20mg ^I	Tab	7 452	6.92	3 261 315.59	12.43	1.80
Lanzor® 15mg ^I	Cap	6 322	5.87	2 072 788.25	0.79	0.13
Pariet® 20mg ^I	Tab	4 401	4.09	1 680 621.53	6.41	1.57
Nexiam® 40mg ^I	Tab	4 060	3.77	1 494 997.59	5.70	1.51
Pantoloc® 40mg ^I	Tab	3 027	2.81	1 260 234.52	4.80	1.71
Ulsec® 20mg ^G	Cap	3 971	3.69	1 225 733.21	4.67	1.27
Losec mups® 10mg ^I	Tab	3 336	3.10	1 010 473.75	3.85	1.24
Controloc® 40mg ^I	Tab	2 510	2.33	988 109.56	3.77	1.62
Pariet® 10mg ^I	Tab	2 864	2.66	825 553.31	3.15	1.18
Gaviscon aniseed® ^I	Sus	9 881	9.18	686 132.53	2.62	0.28
Nexiam® 20mg ^I	Tab	1 924	1.79	538 666.27	2.05	1.15
Ulsanic® ^G	Sus	2 468	2.29	467 543.54	1.78	0.78
Gaviscon advance® ^I	Sus	2 937	2.73	410 966.26	1.57	0.57
Zantac® eff 150mg ^I	Tab	1 838	1.71	366 239.26	1.40	0.82
Pantoloc® 20mg ^I	Tab	1 297	1.20	329 373.03	1.26	1.04
Ulsec® 10mg ^G	Cap	1 380	1.28	300 858.80	1.15	0.89
Ranixhexal® 150mg ^G	Tab	1 881	1.75	298 529.15	1.14	0.65
Mucaine® ^I	Sus	3 198	2.97	252 287.09	0.96	0.32
Lenamet® 400mg ^G	Tab	1 448	1.35	249 644.91	0.95	0.71

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Prevalence % - The number of the specific medicine item claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of the specific medicine item claimed for the specific period (year) divided by the total cost of the total number of acid reducing medicine items for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.5 shows that Lanzor® 30mg was the acid reducer with the highest prevalence (n = 10 643) and cost (n = R4 736 747.05) during 2002. Lanzor® 30mg was also the acid reducer with the highest CPI during 2002 (CPI = 1.83). A CPI > 1 indicates that the specific medicine item was relatively expensive (refer to section 4.6.4). Lanzor® 15mg was the acid reducer in the top 20 with the lowest CPI (CPI = 0.13). Eleven of the top 20 acid reducers have a CPI > 1 and all of these products are PPIs. This indicates that these eleven PPIs were relatively expensive. Esomeprazole (Nexiam® 20mg and Nexiam® 40mg) was introduced to the health care market during 2002. Nexiam® 40mg had the fifth highest cost (n = R1 494 997.59) during 2002 with a CPI of 1.71.

The top 20 acid reducers for 2004

Table 5.6 provides the prevalence of the top 20 acid reducers according to cost for 2004, however the treatment period was not taken into consideration for calculation purposes.

Table 5.6: The prevalence of the top 20 acid reducers for 2004, according to cost.

Trade name	DF	Prevalence	Prevalence %	Cost (R)	Cost %	CPI
Lanzor® 30mg ^I	Cap	10 574	7.81	4 091 488.46	14.66	1.88
Nexiam® 40mg ^I	Tab	10 360	7.65	3 430 848.83	12.29	1.61
Losec mups® 20mg ^I	Tab	6 437	4.75	2 697 546.33	9.66	2.03
Nexiam® 20mg ^I	Tab	8 972	6.63	2 155 314.25	7.72	1.17
Lanzor® 15mg ^I	Cap	6 742	4.98	1 889 423.35	6.77	1.36
Pariet® 20mg ^I	Tab	4 848	3.58	1 825 301.88	6.54	1.83
Pantoloc® 40mg ^I	Tab	5 068	3.74	1 667 550.95	5.97	1.60
Controloc® 40mg ^I	Tab	3 460	2.56	1 201 266.70	4.30	1.68
Gaviscon aniseed® ^I	Sus	11 782	8.70	743 877.69	2.66	0.31
Pantoloc® 20mg ^I	Tab	3 714	2.74	736 821.54	2.64	0.96
Losec mups® 10mg ^I	Tab	2 746	2.03	734 372.36	2.63	1.30
Zantac® eff 150mg ^I	Tab	2 662	1.97	692 443.26	2.48	1.26
Pariet® 10mg ^I	Tab	2 113	1.56	480 035.50	1.72	1.10
Ulsanic® ^I	Sus	2 639	1.95	471 684.54	1.69	0.87
Losec mups® 40mg ^I	Tab	588	0.43	436 977.47	1.57	3.60
Controloc® 20mg ^I	Tab	2 021	1.49	423 604.07	1.52	1.02
Gaviscon advance® ^I	Sus	3 751	2.77	410 186.07	1.47	0.53
Zantac® eff 300mg ^I	Tab	652	0.48	324 468.17	1.16	2.41
Ranixhexal® 150mg ^G	Tab	2 297	1.70	206 136.75	0.74	0.44
Ulsanic® ^I	Tab	1 206	0.89	186 254.66	0.67	0.75

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Prevalence % - The number of the specific medicine item claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of the specific medicine item claimed for the specific period (year) divided by the total cost of the total number of acid reducing medicine items for the corresponding year multiplied by hundred (refer to table 5.2).

Table 5.6 shows that Lanzor® 30mg was again the acid reducer with the highest cost (n = R4 091 488.46) during 2004. Gaviscon aniseed® (antacid) was the acid reducer with the highest prevalence (n = 11 782) during 2004 although it was the acid reducer with the ninth highest total cost (R743 877.69). Gaviscon aniseed® was the acid reducer in the top 20 with the lowest CPI (CPI = 0.31). Losec mups® 40mg was the acid reducer with the highest cost prevalence CPI during 2004 (CPI = 3.60). Seventy percent (n = 14) of the top 20 acid reducers had a CPI > 1 and 85.71 % (n = 12) of these products are PPIs. This indicates that these PPIs were relatively expensive (refer to section 4.6.4). Nexiam® 40mg moved up from the acid reducer fifth highest cost (n = R1 494 997.59) during 2002 to the acid reducer with the second highest cost (n = R3 430 848.83) during 2004. Its CPI increased from 1.51 to 1.61 from 2002 to 2004.

The top 20 acid reducers for 2005

Table 5.7 provides the prevalence of the top 20 acid reducers according to cost for 2005, however the treatment period was not taken into consideration for calculation purposes.

Table 5.7: The prevalence of the top 20 acid reducers for 2005, according to cost.

Trade name	DF	Prevalence	Prevalence %	Cost (R)	Cost %	CPI
Lanzor® 30mg ^I	Cap	5 490	5.93	2 278 151.84	13.48	2.27
Nexiam® 40mg ^I	Tab	5 970	6.45	1 972 059.51	11.67	1.81
Pariet® 20mg ^I	Tab	4 073	4.40	1 721 376.37	10.19	2.32
Controlloc® 40mg ^I	Tab	2 979	3.22	1 071 883.15	6.34	1.97
Nexiam® 20mg ^I	Tab	4 560	4.93	1 068 135.80	6.32	1.28
Zantac® eff 150mg ^I	Tab	3 448	3.72	967 280.67	5.73	1.54
Pantoloc® 40mg ^I	Tab	2 390	2.58	693 198.97	4.10	1.59
Adco-Omeprazole® 20mg ^G	Cap	6 320	6.83	644 191.07	3.81	0.56
Lanzor® 15mg ^I	Cap	2 328	2.51	623 386.51	3.69	1.47
Sandoz Omeprazole® 20mg ^G	Cap	3 458	3.74	490 432.86	2.90	0.78
Zantac® eff 300mg ^I	Tab	954	1.03	483 451.69	2.86	2.78
Losec mups® 20mg ^I	Tab	1 349	1.46	438 381.14	2.59	1.78
Ulsanic® ^I	Sus	2 092	2.26	404 636.56	2.40	1.06
Gaviscon aniseed® ^I	Sus	5 182	5.60	321 299.44	1.90	0.34
Gaviscon advance® ^I	Sus	3 100	3.35	309 914.29	1.83	0.55
Controlloc® 20mg ^I	Tab	1 461	1.58	290 000.59	1.72	1.09
Pariet® 10mg ^I	Tab	1 006	1.09	248 130.57	1.47	1.35
Losec mups® 40mg ^I	Tab	289	0.31	243 808.18	1.44	4.62
Pantoloc® 20mg ^I	Tab	1 416	1.53	243 702.61	1.44	0.94
Altosec® 20mg ^G	Cap	1 625	1.76	208 249.31	1.23	0.70

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Prevalence % - The number of the specific medicine item claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of the specific medicine item claimed for the specific period (year) divided by the total cost of the total number of acid reducing medicine items for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.7 shows that Lanzor® 30mg was still the acid reducer with the highest cost (n = R2 278 151.84) during 2005. Adco-omeprazole® 20mg (generic medicine item) was the acid reducer with the highest prevalence (n = 6320) during 2005. Losec mups® 40mg was the acid reducer with the highest CPI during 2005 (CPI = 4.62). Gaviscon aniseed® was the acid reducer in the top 20 with the lowest CPI (CPI = 0.34). Seventy percent (n = 14) of the top 20 acid reducers had a CPI > 1 and 78.57 % (n = 11) of these products were PPIs. This indicates that these PPIs were relatively expensive (refer to section 4.6.4).

The top 20 acid reducers for 2006

Table 5.8 provides the prevalence of the top 20 acid reducers according to cost for 2006, however the treatment period was not taken into consideration for calculation purposes.

Table 5.8: The prevalence of the top 20 acid reducers for 2006, according to cost.

Trade name	DF	Prevalence	Prevalence %	Cost	Cost %	CPI
Pariet® 20mg ^I	Tab	2 789	4.71	1 307 772.69	12.58	2.67
Nexiam® 40mg ^I	Tab	2 886	4.88	1 239 530.07	11.93	2.44
Zantac® eff 150mg ^I	Tab	3 158	5.34	898595.29	8.65	1.62
Adco-Omeprazole® 20mg ^G	Cap	4 797	8.11	743 695.42	7.16	0.88
Sandoz Omeprazole® 20mg ^G	Cap	3 454	5.84	527 126.51	5.07	0.87
Altosec® 20mg ^G	Cap	3 671	6.21	519 660.34	5.00	0.81
Controloc® 40mg ^I	Tab	1 185	2.00	431 381.45	4.15	2.07
Nexiam® 20mg ^I	Tab	1 375	2.32	396 192.31	3.81	1.64
Zantac® eff 300mg ^I	Tab	804	1.36	379 779.07	3.65	2.69
Topzole® 40mg ^G	Tab	1 041	1.76	333 651.34	3.21	1.82
Lanzor® 30mg ^I	Cap	744	1.26	292 870.45	2.82	2.24
Gaviscon advance® ^I	Sus	2 346	3.97	269 120.91	2.59	0.65
Ulsanic® ^I	Sus	1 078	1.82	246 710.49	2.37	1.30
Pantoloc® 40mg ^I	Tab	577	0.98	210 220.89	2.02	2.07
Lansoloc® 30mg ^G	Tab	2 331	3.94	194 788.45	1.87	0.48
Losec mups® 20mg ^I	Tab	491	0.83	186 080.68	1.79	2.16
Gaviscon aniseed® ^I	Sus	2 580	4.36	174 333.52	1.68	0.38
Adco-Roznal® 30mg ^G	Cap	712	1.20	156 959.55	1.51	1.25
Losec mups® 40mg ^I	Tab	151	0.26	127 596.25	1.23	4.81
Pariet® 10mg ^I	Tab	416	0.70	121 850.73	1.17	1.67

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Prevalence % - The number of the specific medicine item claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of the specific medicine item claimed for the specific period (year) divided by the total cost of the total number of acid reducing medicine items for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.8 shows that Pariet® 20mg was the acid reducer with the highest cost (n = R1 307 772.69) during 2006 and the second highest CPI of 2.67. Adco-omeprazole® 20mg (generic medicine item) was again the acid reducer with the highest prevalence (n = 4797) during 2006. Losec mups® 40mg was the acid reducer with the highest CPI during 2006 (CPI = 4.81). Gaviscon aniseed® was the acid reducer in the top 20 with the lowest CPI (CPI = 0.38). Seventy percent (n = 14) of the top 20 acid reducers had a CPI > 1 and 78.57 % (n = 11) of these products were PPIs. This indicates that these PPIs were relatively expensive (refer to section 4.6.4).

Summary

Lanzor® 30mg was the acid reducer with the highest cost percentage from 2001 to 2005, while Pariet® 20mg took the lead in 2006. Gaviscon aniseed® (antacid) was the acid reducer with the highest prevalence ($n = 11\,782$ in 2004) in the five study years and had the lowest CPI (CPI = 0.26 in 2001) of the top 20 acid reducers during 2001, 2002, 2004, 2005 and 2006. The acid reducer among the top 20 with the highest cost prevalence index (CPI) during the five study years was Losec mups® 40mg (CPI = 4.81) in 2006. PPIs were the sub-pharmacological group with the most products among the top 20, according to cost, during the five study years and had of the highest CPIs.

Table 5.9 provides a summary of the top five acid reducers, according to cost, over the study period (2001 to 2006).

Table 5.9: Summary of the top 5 acid reducers, according to cost, during 2001, 2002, 2004, 2005 and 2006.

Position	2001		2002		2004		2005		2006	
	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI
1	Lanzor [®] 30mg ^I	1.73	Lanzor [®] 30mg ^I	1.83	Lanzor [®] 30mg ^I	1.88	Lanzor [®] 30mg ^I	2.27	Pariet [®] 20mg ^I	2.67
2	Losec mups [®] 20mg ^I	1.80	Losec mups [®] 20mg ^I	1.80	Nexiam [®] 40mg ^I	1.61	Nexiam [®] 40mg ^I	1.81	Nexiam [®] 40mg ^I	2.44
3	Lanzor [®] 15mg ^I	1.25	Lanzor [®] 15mg ^I	0.13	Losec mups [®] 20mg ^I	2.03	Pariet [®] 20mg ^I	2.32	Zantac [®] eff 150mg ^I	2.62
4	Pantoloc [®] 40mg ^I	1.70	Pariet [®] 20mg ^I	1.57	Nexiam [®] 20mg ^I	1.17	Controloc [®] 40mg ^I	1.97	Adco-Omeprazole [®] 20mg ^G	0.88
5	Pariet [®] 20mg ^I	1.39	Nexiam [®] 40mg ^I	1.51	Lanzor [®] 15mg ^I	1.36	Nexiam [®] 20mg ^I	1.28	Sandoz Omeprazole [®] 20mg ^G	0.87

I – Innovator medicine item

G – Generic medicine item

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

The top 5 acid reducers, according to cost, were reasonably constant during the five study years. Nexiam® 40mg was introduced into the market during 2002 and already it appeared among the top 5 acid reducers, according to cost percentage for this period. From 2002 to 2004 Nexiam® 40mg moved from position 5 to position 2 and remained the acid reducer with the second highest cost percentage during 2005 and 2006. Adco-Omeprazole® 20mg and Sandoz-Omeprazole® 20mg were the first generic products to appear among the top 5 acid reducers during 2006. Zantac® effervescent (eff) 150mg was the only H₂RA among the top 5 acid reducers during the study years (table 5.9).

5.5.2.2 PREVALENCE OF ACID REDUCING MEDICINE ACCORDING TO ACTIVE INGREDIENT

The literature study (refer to section 2.5) has shown PPIs to be superior to H₂RAs regarding the clinical efficiency. Since PPIs and H₂RA are the preferred treatment of acid-related disorders only an overview of antacids will be given in this section. From the forgoing discussion it appears that antacids were continuously the second most prescribed acid reducing medicine items (see table 5.2.1). This observation could be due to the fact that most patients who experienced frequent acid-related symptoms do not seek professional medical care (refer to section 1.2) and very often use antacids as self-medication. The average cost per antacids was also much lower than H₂RAs and PPIs which might explain their high prevalence (refer to table 5.2.3).

Figure 5.2 gives the prevalence percentage of acid reducing medicine items according to the active ingredient for the five study years (refer to Appendix A).

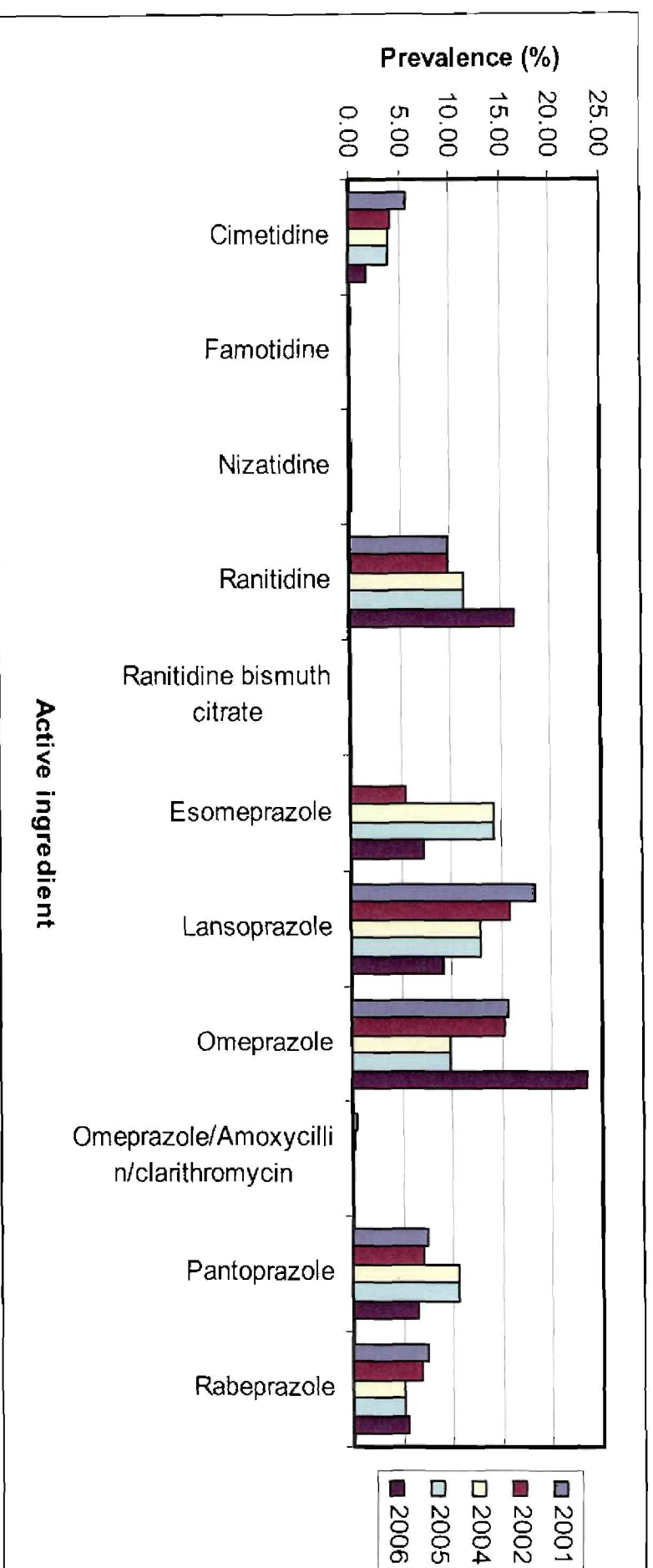


Figure 5.2: The prevalence percentage of acid reducing medicine items according to active ingredient for 2001, 2002, 2004, 2005 and 2006 (refer to Appendix A)..

Figure 5.2 shows that lansoprazole was the active ingredient most often prescribed during 2001 and 2002. Lansoprazole represented 18.39 % (n = 14 855) in 2001 and 15.76 % (n = 16 955) in 2002 of all acid reducing medicine items prescribed respectively during 2001 (n = 80 773) and 2002 (n = 107 637). Esomeprazole represents 14.28 % (n = 19 332) of all acid reducing medicine items (n = 135 401) prescribed during 2004 and was the active ingredient with the highest prevalence for 2004. Omeprazole was the active ingredient with the highest prevalence in 2005 and 2006. Omeprazole represented 16.88 % (n = 15 627) of all acid reducing medicine items prescribed (n = 92 565) in 2005 and 23.34 % (n = 13 808) in 2006 of all acid reducing medicine items prescribed (n = 59 157) in 2006 (refer to Appendix A).

As shown by figure 5.2 ranitidine represents the active ingredient among the H₂RAs with the highest prevalence for 2001, 2002, 2004, 2005 and 2006. Famotidine represented 0.10%, 0.07% and 0.08% of the total number of acid reducing medicine items claimed respectively for 2001, 2002 and 2004. Medicine items, containing famotidine as active ingredient, were not present on the database for 2005 and 2006. It is not known whether the absence of famotidine was due to the active ingredient not being present on the medicine claims database or whether the active ingredient was not available on the market anymore during 2005 and 2006. Nizatidine represented 0.06%, 0.17%, 0.17%, 0.19% and 0.16% of the total number of acid reducing medicine items claimed respectively during 2001, 2002, 2004, 2005 and 2006. Ranitidine bismuth citrate was only present on the medicine claims database during 2002 and represented 0.33 % (n = 107 637) of the total number of acid reducing medicine items prescribed (Appendix A).

5.5.3 PREVALENCE, AVERAGE COST AND TOTAL COST OF INDIVIDUAL ACID REDUCING MEDICINE ITEMS

In the following section the focus was on the prevalence, average cost and total cost of individual histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs). Tables that summarise the prevalence, average cost and total cost of individual H₂RAs and PPIs appear in Appendix B.

5.5.3.1 PREVALENCE, AVERAGE COST AND TOTAL COST OF H₂RA

In this section an overview will be given of the prevalence, average cost and total cost of individual H₂RA for the five study years.

Cimetidine

Lenamet® 400mg was the product, containing cimetidine, that had the highest prevalence during 2001 (n = 1 191), 2002 (n = 1 448), 2004 (n = 1 569) and 2005 (n = 709). During 2006 Adco-cimetidine® 400mg had the highest prevalence (n = 440). Tagamet® 200mg tablets had the highest average cost of R352.19±367.44 during 2001 and Tagamet® 400mg had the highest average cost from 2002 to 2006. The average cost of Tagamet® 400mg decreased from 2002 (R264.24±117.92) to 2004 (R221±231.98) and to 2005 (R118.49±213.46). From 2005 to 2006 the average cost of Tagamet® 400mg prescription increased with practical significance (d = 0.80) (refer to section 4.7.3.4) (Appendix B).

Table 5.10 provides a summary of the medicine items, containing cimetidine as an active ingredient; with CPI > 1 (refer to section 4.6.4).

Table 5.10: Summary of medicine items, containing cimetidine as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Tagament S® 200mg ^I	Syr	1.51	-	-	-	-
Tagament® 200mg ^I	Tab	1.53	-	-	-	-
Tagament® 400mg ^I	Tab	1.19	1.08	1.07	-	1.94
Duomet® 400mg ^G	Tab	1.03	1.15	-	-	-
Ulcim® 400mg ^G	Tab	-	1.06	-	-	-

DF -- Dosage form

I -- Innovator medicine item

G -- Generic medicine item

Table 5.10 shows that Tagamet® 400mg was the medicine item, containing cimetidine as active ingredient that had a CPI > 1 for the most years. If the CPI > 1 it indicates that these medicine items were relatively expensive (refer to section 4.6.4). During 2005 all the cimetidine containing products had a CPI < 1, therefore relatively inexpensive.

Table 5.11 provides an overview of the prevalence, average cost and total cost of medicine items containing cimetidine as active ingredient for the five study years.

Table 5.11: The prevalence, average cost and total cost of medicine items containing cimetidine as active ingredient for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Cimetidine 200mg	Syr	1	0.02	346.77	0.00	346.77
	Cimetidine 200mg	Amp	2	0.04	31.03	3.77	62.05
	Cimetidine 200mg	Tab	1 222	26.30	82.94	83.69	101 347.50
	Cimetidine 400mg	Tab	3 421	73.63	184.24	86.98	630 277.51
2002	Cimetidine 200mg	Tab	1 487	27.97	65.29	37.07	97081.58
	Cimetidine 400mg	Tab	3 830	72.03	180.92	91.67	692 935.69
2004	Cimetidine 200mg	Amp	8	0.15	57.86	53.71	462.89
	Cimetidine 200mg	Tab	1 451	27.42	35.06	28.49	50 872.50
	Cimetidine 400mg	Tab	3 833	72.43	81.25	85.66	311 435.44
2005	Cimetidine 200mg	Amp	1	0.04	15.93	0.00	15.93
	Cimetidine 200mg	Tab	573	22.87	19.91	15.01	11 409.72
	Cimetidine 400mg	Tab	1 931	77.09	30.45	28.54	58 807.99
2006	Cimetidine 200mg	Tab	182	17.28	21.67	15.63	3 943.15
	Cimetidine 400mg	Tab	871	82.72	32.61	28.56	284 02.18

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of cimetidine containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.11 shows that the average cost of cimetidine 400mg tablets revealed a practical significant decrease ($d > 0.8$) from 2001 to 2004 ($d = 1.18$), from 2001 to 2005 ($d = 1.768$) and from 2001 to 2006 ($d = 1.74$). From 2001 to 2005 the average cost of cimetidine 200mg ampoules revealed a practical significant decrease ($d = 4.00$) (refer to section 4.7.3.4).

Famotidine

Famotidine containing medicine items were only present on the medicine claims database from 2001 to 2004. As previously explained it is not known whether the absence of famotidine was due to the active ingredient not being present on the medicine claims database or whether the active ingredient was not available on the market anymore during 2005 and 2006. Pepsid® 40mg had the highest prevalence during 2004 ($n = 107$) and the highest average cost (R601.91±191.01) during 2001 (Appendix B).

Table 5.12 provides a summary of the medicine items, containing famotidine as active ingredient; with CPI > 1 (refer to section 4.6.4).

Table 5.12: Summary of medicine items, containing famotidine as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Pepsid® 20mg ^I	Tab	1.11	-	-	-	-
Pepsid® 40mg ^I	Tab	2.62	1.89	2.35	-	-

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.12 shows that Pepsid® 40mg had a CPI > 1 from 2001 to 2004. Thus Pepsid® 40mg had a CPI > 1 for all the study years it appeared on the database. If the CPI > 1 it indicates that these medicine items were relatively expensive (refer to section 4.6.4).

Table 5.13 provides an overview of the prevalence, average cost and total cost of medicine items, containing famotidine as active ingredient, for the five study years.

Table 5.13: The prevalence, average cost and total cost of medicine items, containing famotidine as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Famotidine 20mg	Tab	40	47.62	255.89	101.74	10 235.59
	Famotidine 40mg	Tab	44	52.38	601.91	191.01	26 484.20
2002	Famotidine 20mg	Tab	4	5.63	117.79	49.98	471.15
	Famotidine 40mg	Tab	67	94.37	460.60	369.22	30 859.96
2004	Famotidine 40mg	Tab	107	100.00	484.60	100.72	51 851.67

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of famotidine containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.13 shows that the average cost of famotidine 20mg tablets revealed a practical significant decrease ($d > 0.8$) from 2001 to 2002 ($d = 1.36$) (refer to section 4.7.3.4).

Nizatidine

Antazid® 150mg was the only medicine item, containing nizatidine as active ingredient. Antazid® 150mg had the highest prevalence during 2004 ($n = 233$) and the highest average cost during 2002 ($R248.18 \pm 149.56$) (Appendix B).

Table 5.14 provides a summary of the medicine items, containing nizatidine as active ingredient, with CPI > 1 (refer to section 4.6.4).

Table 5.14: Summary of medicine items, containing nizatidine as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Antazid® 150mg ^I	Cap	1.06	1.02	1.08	-	-

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.14 shows that Antazid® 150mg had a CPI > 1 for 2001, 2002 and 2004. The CPI of Antazid® 150mg stayed reasonably constant during these years. If the CPI > 1 it indicates that these medicine items were relatively expensive (refer to section 4.6.4).

Table 5.15 provides an overview of the prevalence, average cost and total cost of medicine items, containing nizatidine as active ingredients, for the five study years.

Table 5.15: The prevalence, average cost and total cost of medicine items, containing nizatidine as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Nizatidine 150mg	Cap	45	100.00	243.82	209.52	10 971.91
2002	Nizatidine 150mg	Cap	183	100.00	248.18	149.56	45 416.38
2004	Nizatidine 150mg	Cap	233	100.00	221.78	134.62	51 674.85
2005	Nizatidine 150mg	Cap	174	100.00	174.67	94.60	30 392.10
2006	Nizatidine 150mg	Cap	95	100.00	120.87	41.63	11 482.42

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of nizatidine containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.15 shows that the average cost of nizatidine 150mg increased from 2001 to 2002 and then decreased from 2002 to 2006. The effect sizes (d-values) were of no significant value (refer to section 4.7.3.4).

Ranitidine

Appendix B shows that Zantac® 150mg effervescent tablets had the highest prevalence for 2001 (n = 1 501), 2002 (n = 1 838), 2004 (n = 2 662), 2005 (n = 3 448) and 2006 (n = 3 158). Thus Zantac® 150mg effervescent tablets had the highest prevalence for all the study years and while Zantac® 300mg effervescent tablets had the highest average cost for all the study years. The average cost of Zantac® 300mg effervescent tablets increased from 2001 (R427.16±135.16) to

2006 (R548.29±381.47). This increase was, however, of no practical significance ($d < 0.8$) (refer to section 4.7.3.4). Apo-ranitidine® 150mg tablets (R242.46±82.82) and Histak® 75mg (R93.97±63.77) tablets were generic medicine items with average cost higher than the average cost of the innovator medicine items respectively Zantac® 150mg tablets (R240.07±112.59) and Zantac® 75mg tablets (R83.76±43.02) during 2001. From 2002 to 2004 the average cost of Zantac® 150mg tablets, Zantac® 300mg tablets, Zantac® 150mg effervescent tablets and Zantac® 300mg effervescent tablets increased. A possible explanation for this increase might be that the manufacturer, of the above mentioned innovator medicine items, increased the average cost of these medicine items to compensate for the possible loss incurred, due to generic substitution.

Table 5.16 provides a summary of the medicine items, containing ranitidine as active ingredient, with CPI > 1 (refer to section 4.6.4).

Table 5.16: Summary of medicine items, containing ranitidine as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Zantac® ^I	Inj	1.18	-	-	-	-
Zantac® ^I	Syr	-	-	-	-	1.49
Zantac® 150mg ^I	Tab	1.04	1.02	1.55	1.66	2.29
Apo-ranitidine® 150mg ^G	Tab	1.05	-	-	-	-
Zantac® 300mg ^I	Tab	1.36	1.50	2.45	3.31	3.12
Apo-ranitidine® 300mg ^G	Tab	1.22	-	-	-	-
Histak® 300mg ^G	Tab	1.11	-	-	-	-
Ranixhexal® 300mg ^G	Tab	1.01	-	-	-	-
Ulcaid® 300mg ^G	Tab	1.05	1.09	1.42	-	-
Zantac® 150mg eff ^I	Tab	-	-	1.26	1.55	1.62
Zantac® 300mg eff ^I	Tab	1.86	1.76	2.41	2.79	2.69

DF -- Dosage form

I -- Innovator medicine item

G -- Generic medicine item

Table 5.16 shows that Zantac® 150mg tablets, Zantac® 300mg tablets and Zantac® 300mg effervescent tablets had CPI > 1 for all the study years. Zantac® 300mg tablets had the highest CPI during 2005. If the CPI > 1 it indicates that these medicine items were relatively expensive (refer to section 4.6.4).

Table 5.17 provides an overview of the prevalence, average cost and total cost of medicine items, containing ranitidine as active ingredient, for the five study years.

Table 5.17: The prevalence, average cost and total cost of medicine items, containing ranitidine as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Ranitidine	Syr	42	0.54	172.28	99.74	7 235.81
	Ranitidine 2ml/50mg	Inj	6	0.08	270.48	190.52	1 622.89
	Ranitidine 75mg	Tab	1 027	13.11	82.04	44.50	84 251.48
	Ranitidine 150mg	Tab	3 683	47.03	179.76	100.73	662 049.85
	Ranitidine 300mg	Tab	1 366	17.44	233.40	102.29	318 828.96
	Ranitidine eff 150mg	Tab	1 501	19.17	159.01	84.20	238 666.59
	Ranitidine eff 300mg	Tab	206	2.63	427.16	135.16	87 994.10
2002	Ranitidine	Syr	37	0.35	225.23	134.91	8 333.33
	Ranitidine 2ml/50mg	Inj	6	0.06	219.99	221.48	1 319.91
	Ranitidine 75mg	Tab	1 433	13.59	75.11	44.32	107 627.94
	Ranitidine 150mg	Tab	5 061	48.00	169.94	98.66	860 074.33
	Ranitidine 300mg	Tab	1 790	16.98	203.36	120.33	364 010.00
	Ranitidine eff 150mg	Tab	1 838	17.43	199.26	110.60	366 239.26
	Ranitidine eff 300mg	Tab	378	3.59	428.95	151.01	162 142.35
2004	Ranitidine	Syr	76	0.50	166.85	132.61	12 680.65
	Ranitidine 2ml/50mg	Inj	99	0.65	125.46	205.40	12 420.69
	Ranitidine 75mg	Tab	754	4.95	49.92	36.05	37 637.17
	Ranitidine 150mg	Tab	7 645	50.20	91.19	95.85	697 158.19
	Ranitidine 300mg	Tab	3 178	20.87	141.74	151.08	450 465.58
	Ranitidine eff 75mg	Tab	163	1.07	62.78	50.40	10 233.36
	Ranitidine eff 150mg	Tab	2 662	17.48	260.12	156.84	692 443.26
	Ranitidine eff 300mg	Tab	652	4.28	497.65	217.61	324 468.17

Table 5.17 (Continued): The prevalence, average cost and total cost of medicine items, containing ranitidine as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2005	Ranitidine	Syr	41	0.33	207.48	171.86	8 506.77
	Ranitidine 2ml/50mg	Inj	119	0.95	192.51	352.98	22 908.30
	Ranitidine 75mg	Tab	388	3.08	50.08	39.20	19 432.23
	Ranitidine 150mg	Tab	4 822	38.34	63.02	76.15	303 859.75
	Ranitidine 300mg	Tab	2 736	21.75	89.29	162.61	244 285.80
	Ranitidine eff 75mg	Tab	70	0.56	69.99	35.61	4 899.48
	Ranitidine eff 150mg	Tab	3 448	27.41	280.53	163.22	967 280.67
	Ranitidine eff 300mg	Tab	954	7.58	506.76	193.46	483 451.69
2006	Ranitidine	Syr	15	0.16	261.31	158.69	3 919.60
	Ranitidine 2ml/50mg	Inj	82	0.85	168.48	262.39	13 814.95
	Ranitidine 75mg	Tab	207	2.14	57.59	40.52	11 920.59
	Ranitidine 150mg	Tab	3 402	35.25	68.42	76.69	232 759.11
	Ranitidine 300mg	Tab	1 890	19.58	61.06	94.78	115 393.01
	Ranitidine eff 75mg	Tab	94	0.97	99.85	60.94	9 386.17
	Ranitidine eff 150mg	Tab	3 158	32.72	284.55	169.79	898 595.29
	Ranitidine eff 300mg	Tab	804	8.33	472.36	199.39	379 779.07

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of ranitidine containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.17 shows that the average cost of ranitidine 150mg tablets revealed a practical significant decrease ($d > 0.8$) from 2001 to 2004 ($d = 0.88$), from 2001 to 2005 ($d = 1.16$) and from 2001 to 2006 ($d = 1.11$). The average cost of ranitidine 300mg tablets decreased significantly from 2001 to 2005 ($d = 0.89$) and from 2001 to 2006 ($d = 1.68$) (refer to section 4.7.3.4).

Ranitidine bismuth citrate

Appendix B shows Pylorid® 400mg tablets were only present during 2002 on the database. It is not known whether the absence of ranitidine bismuth citrate was due to the active ingredient not being present on the medicine claims database or whether the active ingredient was not available on the market anymore during 2004, 2005 and 2006. The CPI of Pylorid® 400mg tablets (CPI = 1.18) was greater than one and therefore it might be assumed that this therapy was relatively expensive during 2002 (refer to section 4.6.4).

Table 5.18 provides an overview of the prevalence, average cost and total cost of medicine items, containing ranitidine bismuth citrate as active ingredient, for the five study years.

Table 5.18: The prevalence, average cost and total cost of medicine items, containing ranitidine bismuth citrate as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2002	Ranitidine bismuth citrate	Tab	33	100.00	288.23	82.04	9511.46

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of ranitidine bismuth citrate containing medicine items claimed for the corresponding year multiplied by hundred.

Summary

Table 5.19 provides a summary of the top five H₂RAs, according to cost, for the five study years.

Table 5.19: Summary of the top 5 H₂RAs, according to cost, for 2001, 2002, 2004, 2005 and 2006 (refer to Appendix C).

Position	2001		2002		2004		2005		2006	
	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI	Medicine item	CPI
1	Zantac [®] eff 150mg ^I	0.92	Zantac [®] eff 150mg ^I	1.17	Zantac [®] eff 150mg ^I	2.01	Zantac [®] eff 150mg ^I	1.99	Zantac [®] eff 150mg ^I	1.80
2	Lenamet [®] 400mg ^G	1.01	Ranhexal [®] 150mg ^G	0.93	Zantac [®] eff 300mg ^I	3.84	Zantac [®] eff 300mg ^I	3.59	Zantac [®] eff 300mg ^I	2.98
3	Ranhexal [®] 150mg ^G	0.94	Lenamet [®] 400mg ^G	1.01	Ranhexal [®] 150mg ^G	0.69	Zantac [®] 300mg ^I	4.26	Ranhexal [®] 150mg ^G	0.58
4	Adco-cimetidine [®] 400mg ^G	1.13	Histak [®] 150mg ^G	1.22	Histak [®] 150mg ^G	0.54	Ranhexal [®] 150mg ^G	0.51	Histak [®] 150mg ^G	0.27
5	Ranhexal [®] 300mg ^G	1.35	Ultak [®] 150mg ^G	0.71	Ultak [®] 150mg ^G	0.55	Zantac [®] 150mg ^I	2.14	Ultak [®] 300mg ^G	0.34

I – Innovator medicine item

G – Generic medicine item

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.19 shows that Zantac® 150mg effervescent tablets were the H₂RA, with the highest total cost, during the five study years. Zantac® 300mg effervescent tablets were the H₂RA, with the second highest total cost, from 2004 to 2006. Ranihexal® 150mg appeared among the top five of H₂RAs although it had a CPI < 1 for all five study years. The CPI of Ranihexal® 150mg decreased from 2001 to 2006. During 2005 the following four medicine items of the top five of H₂RAs were innovators: Zantac® effervescent 300mg, Ranihexal® 150mg, Histak® 150mg and Ultak® 300mg. These medicine items had the same active ingredient.

5.5.3.2 PREVALENCE, AVERAGE COST AND TOTAL COST OF PPIs

In the following section an overview will be given of the prevalence, average cost and total cost of individual PPIs for the five study years (refer to Appendix B).

Esomeprazole

Nexiam® tablets (20mg and 40mg) were introduced into the market during 2002. While Nexiam® IV (intravenous) was introduced into the market during 2005. Nexiam® 20mg had the highest prevalence (n = 8 972) during 2004 and had the highest average cost (R288.14±90.59) during 2006. Nexiam® 40mg had the highest prevalence (n = 10 360) during 2004 and had the highest average cost (R429.50±126.91) during 2006 (refer to Appendix B).

Table 5.20 provides a summary of the products, containing esomeprazole as active ingredient; with CPI > 1 (refer to section 4.6.4).

Table 5.20: Summary of products, containing esomeprazole as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Nexiam® 20mg ^I	Tab	-	1.15	1.17	1.29	1.64
Nexiam® 40mg ^I	Tab	-	1.51	1.61	1.82	2.44
Nexiam® ^I	IV	-	-	-	1.05	1.24

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.20 shows that Nexiam® 20mg and Nexiam® 40mg had a CPI greater than one for 2002, 2004, 2005 and 2006. Nexiam® IV (intravenous) had a CPI greater than one for 2005 and 2006. Therefore it might be assumed that Nexiam® therapy was relatively expensive during the five study years (refer to section 4.7.3.4). Nexiam® 40mg was the product, containing esomeprazole that had the highest CPI (CPI = 2.44) during 2006.

Table 5.21 provides an overview of the prevalence, average cost and total cost of medicine items, containing esomeprazole as active ingredient, for the five study years.

Table 5.21: The prevalence, average cost and total cost of medicine items, containing esomeprazole as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2002	Esomeprazole 20mg	Tab	1 924	32.15	279.97	98.81	538 666.27
	Esomeprazole 40mg	Tab	4 060	67.85	368.23	160.21	1 494 997.59
2004	Esomeprazole 20mg	Tab	8 972	46.41	240.23	89.23	2 155 314.28
	Esomeprazole 40mg	Tab	10 360	53.59	331.16	156.55	3 430 848.83
2005	Esomeprazole 20mg	Tab	4 560	43.30	234.24	79.62	1 068 135.80
	Esomeprazole 40mg	Tab	5 970	56.68	330.33	150.26	1 972 059.51
	Esomeprazole	Inj	2	0.02	190.77	41.15	381.54
2006	Esomeprazole 20mg	Tab	1 375	32.17	288.14	90.59	396 192.31
	Esomeprazole 40mg	Tab	2 886	67.52	429.50	126.91	1 239 530.07
	Esomeprazole	Inj	13	0.30	217.79	19.62	2 831.33

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of esomeprazole containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.21 shows that the average cost of esomeprazole 20mg and esomeprazole 40mg decreased from 2002 to 2005 and increased from 2005 to 2006. The effect sizes (d-values) were of no significant value (refer to section 4.7.3.4).

Lansoprazole

Lanzor® 15mg and Lanzor® 30mg capsules were the only products, containing lansoprazole, which appeared on the database during 2001 to 2002. From 2004, 2005 and 2006 Lanzor HB® was present on the database. Lanzor HB® is schedule 2, but contains lansoprazole 15mg (Snyman, 2007:230). According to The Medicines and Related Substances Act (Act 101 of 1965) Lanzor HB® may be used as over-the-counter (OTC) medication. During 2005 and 2006 a generic medicine item (Lansoloc® OTC) was available. A number of generic medicine items for Lanzor® 15mg and Lanzor® 30mg capsules became available during 2005 (refer to Appendix B).

Table 5.22 provides a summary of the products, containing lansoprazole as active ingredient, with CPI > 1 (refer to section 4.6.4).

Table 5.22: Summary of products, containing lansoprazole as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Lanzor® 15mg ^I	Cap	1.25	1.35	1.36	1.47	1.61
Lanzor® 30mg ^I	Cap	1.73	1.83	1.88	2.29	2.24

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.22 shows that Lanzor® 15mg and Lanzor® 30mg had a CPI greater than one for the five study years. Therefore it might be assumed that Lanzor® 15mg and Lanzor® 30mg therapy were relatively expensive during the five study years (refer to section 4.7.3.4)

Table 5.23 provides an overview of the prevalence, average cost and total cost of medicine items, containing lansoprazole as active ingredient, for the five study years

Table 5.23: The prevalence, average cost and total cost of medicine items, containing lansoprazole as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Lansoprazole 15mg	Cap	5 151	34.68	287.33	78.86	1 480 051.48
	Lansoprazole 30mg	Cap	9 704	65.32	398.42	151.63	3 866 295.47
2002	Lansoprazole 15mg	Cap	6 322	37.26	327.87	74.55	2 072 788.25
	Lansoprazole 30mg	Cap	10 643	62.74	445.06	161.52	4 736 747.05
2004	Lansoprazole 15mg	Cap	6 809	39.17	278.79	95.91	1 898 256.77
	Lansoprazole 30mg	Cap	10 574	60.83	386.94	164.00	4 091 488.46
2005	Lansoprazole 15mg	Cap	2 821	30.79	242.99	108.79	6 85 466.74
	Lansoprazole 30mg	Cap	6 342	69.21	377.33	173.11	2 393 004.69
2006	Lansoprazole 15mg	Cap	1 143	21.12	130.19	130.64	148 806.14
	Lansoprazole 30mg	Cap	4 270	78.88	157.89	178.60	674 190.71

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of lansoprazole containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.23 shows that the average cost of lansoprazole 15mg and lansoprazole 30mg increased from 2001 to 2002 and decreased from 2002 to 2006. The average cost of lansoprazole 15mg capsules revealed a practical significant decrease ($d > 0.8$) from 2001 to 2006 ($d = 1.20$) and from 2004 to 2006 ($d = 1.14$). The average cost of lansoprazole 30mg capsules decreased significantly from 2001 to 2006 ($d = 1.35$) and from 2004 to 2006 ($d = 1.28$) (refer to section 4.7.3.4).

Omeprazole

Appendix B shows Losec mups® 20mg was the product, containing omeprazole, with the highest prevalence for 2001 (n = 8 361), 2002 (n = 7 452) and 2004 (n = 6 437). While Adco-omeprazole® 20mg was the omeprazole containing product with the highest prevalence for 2005 (n = 6 320) and 2006 (n = 4 797). Losec mups® 40mg had the highest average cost during 2001 (R630.56±283.43), 2002 (R738.17±409.75) and 2005 (R843.63±292.91). Losec® infusion was the omeprazole containing product with the highest average cost during 2004 and 2006. The average cost of Losec® infusion decreased from 2004 (R2017.59±1012.60) to 2005 (R526.36±543.70) and increased to 2006 (R1005.62±1921.70). While there was only one generic product (Ulsec®) available for Losec mups® 10mg and Losec mups® 20mg during 2001 and 2002, a number of generic products became available during 2004.

Table 5.24 provides a summary of medicine items, containing omeprazole as active ingredient; with CPI > 1 (refer to section 4.6.4).

Table 5.24: Summary of medicine items, containing omeprazole as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Losec mups® 10mg ^I	Tab	1.24	1.24	1.30	1.16	1.11
Losec mups® 20mg ^I	Tab	1.80	1.80	2.03	1.79	2.16
Ulsec® 20mg ^G	Cap	1.33	1.27	1.42	-	-
Losec mups® 40mg ^I	Tab	2.74	3.03	3.60	4.65	4.80
Omez® 40mg ^G	Cap	-	-	-	-	1.19
Losec® Infus ^I	Inj	-	-	9.79	2.90	5.72

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.24 shows that Losec mups® 10mg, Losec mups® 20mg and Losec mups® 40mg had CPI > 1 for all the study years. Losec® infusion had the highest prevalence (CPI = 9.79) during 2004 of all the CPI through the study years. Therefore it might be assumed that therapy with Losec mups® 10mg, Losec mups® 20mg and Losec mups® 40mg was relatively expensive during the five study years (refer to section 4.7.3.4).

Table 5.25 provides an overview of the prevalence, average cost and total cost of medicine items, containing omeprazole as active ingredient, for the five study years.

Table 5.25: The prevalence, average cost and total cost of medicine items, containing omeprazole as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std dev $\pm$	Total cost (R)
2001	Omeprazole 10mg	Tab	3 354	26.43	286.17	77.92	959 827.11
	Omeprazole 10mg	Cap	153	1.21	210.27	82.76	32 240.29
	Omeprazole 20mg	Tab	8 361	65.89	413.35	152.36	3 456 060.37
	Omeprazole 20mg	Cap	518	4.08	305.14	161.27	158 061.25
	Omeprazole 40mg	Tab	303	2.39	630.56	283.43	191 060.01
2002	Omeprazole 10mg	Tab	3 336	20.43	302.90	89.25	1 010 473.75
	Omeprazole 10mg	Cap	1 380	8.45	218.01	74.59	300 858.80
	Omeprazole 20mg	Tab	7 452	45.65	437.64	170.57	3 261 315.59
	Omeprazole 20mg	Cap	3 971	24.32	308.67	125.90	1 225 733.21
	Omeprazole 40mg	Tab	186	1.14	738.17	409.75	137 299.35
2004	Omeprazole 10mg	Tab	2 746	20.66	267.43	102.54	734 372.36
	Omeprazole 10mg	Cap	112	0.84	121.12	66.40	13 565.08
	Omeprazole 20mg	Tab	6 437	48.43	419.07	193.92	26 97 546.33
	Omeprazole 20mg	Cap	3 400	25.58	113.44	74.67	385 693.91
	Omeprazole 40mg	Tab	588	4.42	743.16	360.47	436 977.47
	Omeprazole	Inj	8	0.06	2 017.59	1012.60	16 140.68
2005	Omeprazole 10mg	Tab	870	5.57	210.53	84.81	183 159.89
	Omeprazole 10mg	Cap	524	3.35	124.96	47.83	65 476.92
	Omeprazole 20mg	Tab	1 349	8.63	324.97	188.09	438 381.14
	Omeprazole 20mg	Cap	12 586	80.54	117.32	67.76	1 476 605.36
	Omeprazole 40mg	Tab	289	1.85	843.63	292.91	243 808.18
	Omeprazole	Inj	9	0.06	526.36	543.70	4 737.23
2006	Omeprazole 10mg	Tab	212	1.54	194.43	166.41	41 220.13
	Omeprazole 10mg	Cap	380	2.75	135.98	45.75	51 673.56
	Omeprazole 20mg	Tab	491	3.56	378.98	197.13	186 080.68
	Omeprazole 20mg	Cap	12 551	90.90	149.74	45.86	1 879 427.71
	Omeprazole 40mg	Tab	151	1.09	845.01	284.88	127 596.25
	Omeprazole 40mg	Cap	2	0.01	209.31	98.66	418.61
	Omeprazole	Inj	21	0.15	1 005.62	1921.70	21 118.00

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of omeprazole containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.25 shows that the average cost of omeprazole 10mg capsules (generic medicine items) revealed a practical significant decrease ($d > 0.8$) from 2001 to 2004 ($d = 1.07$), from 2001 to 2005 ($d = 1.03$) and from 2001 to 2006 ($d = 0.90$). The average cost of omeprazole 10mg tablets (Losec mups® 10mg) decreased significantly from 2001 to 2005 ($d = 0.89$). The average cost of omeprazole 20mg capsules (generic medicine items) decreased significantly from 2001 to 2004 ($d = 1.89$), from 2001 to 2005 ($d = 1.16$) and from 2001 to 2006 ($d = 0.963$). The

average cost of omeprazole injection (Losec® Infus) decreased significantly from 2004 to 2005 ($d = 1.47$) (refer to section 4.7.3.4).

Omeprazole/amoxicillin/clarithromycin

Losec 20 Triple pack®, is a PPI-based three-drug regimen (refer to section 2.5.2.6) to eradicate *Helicobacter pylori* (*H.pylori*), containing omeprazole, amoxicillin and clarithromycin as active ingredient.

Appendix B shows that Losec 20 Triple pack® was only prescribed during 2001, 2002, 2004 and 2005. It is not known whether the absence of Losec 20 Triple pack® during 2006 was due to the medicine item not being present on the medicine claims database or whether the medicine item was not available on the market anymore. Losec 20 Triple pack® had a CPI greater than one for the five study years. Therefore it might be assumed that Losec 20 Triple pack® therapy was relatively expensive during the five study years (refer to section 4.7.3.4)

Table 5.26 provides an overview of the prevalence, average cost and total cost of omeprazole/amoxicillin/clarithromycin containing medicine items, for the five study years.

Table 5.26: The prevalence, average cost and total cost of omeprazole/amoxicillin/clarithromycin containing medicine items, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Omeprazole/amoxicillin/clarithromycin	Cap	266	100.00	678.84	121.38	180 572.15
2002	Omeprazole/amoxicillin/clarithromycin	Cap	278	100.00	740.31	99.83	205 806.22
2004	Omeprazole/amoxicillin/clarithromycin	Cap	46	100.00	676.80	194.10	311 32.77
2005	Omeprazole/amoxicillin/clarithromycin	Cap	2	100.00	609.90	0.00	1 219.80

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of omeprazole/amoxicillin/clarithromycin containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.26 shows that the average cost of omeprazole/amoxicillin/clarithromycin containing medicine item (Losec 20 Triple pack®) increased from 2001 to 2002 and decreased from 2002

to 2005. The effect sizes (d-values) calculated between the average cost per medicine item between the different years were of no significant value (refer to section 4.7.3.4).

Pantoprazole

Appendix B shows Pantoloc® 40mg was the medicine item, containing pantoprazole, with the highest prevalence during 2001 (n = 3 384), 2002 (n = 3 027) and 2004 (n = 5 068). While Controlloc® 40mg was the medicine item, containing pantoprazole, with the highest prevalence during 2005 (n = 2 979) and 2006 (n = 1 185). Pantoloc® 40mg was the medicine item, containing pantoprazole, with the highest average cost during 2001 (R391.47±141.87), 2002 (R416.33±138.81) and 2006 (R364.33±133.95). Pantoloc® injection was the medicine item, containing pantoprazole, that had the highest average cost during 2004. The average cost of Pantoloc® injections increased with 183.06% from 2002 (R330.84±0.00) to 2004 (R935.62±1058.55). Controlloc® 40mg was the medicine item, containing pantoprazole, that had the highest average cost during 2005 (R359.81±110.35). Generic medicine items were available during 2006. The average cost of Pantoloc® 20mg, innovator medicine item, (R184.32±56.98) and Topzole® 20mg, generic medicine item, (R184.24±59.99) were basically the same during 2006. The average cost of Pantoloc® 40mg (R364.33±133.95) and Controlloc® 40mg (R364.03±90.78) were also similar during 2006.

Table 5.27 provides a summary of medicine items, containing pantoprazole as active ingredient, with CPI > 1 (refer to section 4.6.4).

Table 5.27: Summary of medicine items, containing pantoprazole as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Controlloc® 20mg ^I	Tab	1.08	1.03	1.02	1.09	1.17
Pantoloc® 20mg ^I	Tab	1.08	1.04	-	-	1.05
Topzole® 20mg ^G	Tab	-	-	-	-	1.05
Controlloc® 40mg ^I	Tab	1.62	1.62	1.68	1.98	2.07
Pantoloc® 40mg ^I	Tab	1.70	1.71	1.60	1.60	2.07
Topzole® 40mg ^G	Tab	-	-	-	-	1.82
Pantoloc® ^I	Inj	1.22	1.36	4.54	-	1.01

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.27 shows that Controlloc® 20mg, Controlloc® 40mg and Pantoloc® 40mg had CPI > 1 for all the study years. During 2006 all the pantoprazole containing products had CPI > 1.

Therefore it might be assumed that pantoprazole therapy was relatively expensive during the five study years (refer to section 4.7.3.4).

Table 5.28 provides an overview of the prevalence, average cost and total cost of medicine items, containing pantoprazole as active ingredient, for the five study years.

Table 5.28: The prevalence, average cost and total cost of medicine items, containing pantoprazole as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Pantoprazole 20mg	Tab	468	7.82	249.39	83.15	116 713.16
	Pantoprazole 40mg	Tab	5 517	92.17	383.90	135.99	2 117 996.54
	Pantoprazole	Inj	1	0.02	279.69	0.00	279.69
2002	Pantoprazole 20mg	Tab	2 014	26.67	252.52	70.18	508 576.22
	Pantoprazole 40mg	Tab	5 537	73.32	406.58	140.57	2 248 344.08
	Pantoprazole	Inj	1	0.01	330.84	0.00	330.84
2004	Pantoprazole 20mg	Tab	5 735	40.20	202.34	71.19	1 160 425.61
	Pantoprazole 40mg	Tab	8 528	59.78	336.40	142.53	2 868 817.65
	Pantoprazole	Inj	3	0.02	935.62	1 058.55	2 806.86
2005	Pantoprazole 20mg	Tab	2 877	34.85	185.51	59.03	533 703.20
	Pantoprazole 40mg	Tab	5 369	65.04	328.75	111.97	1 765 082.12
	Pantoprazole	Inj	9	0.11	159.70	60.30	1 437.31
2006	Pantoprazole 20mg	Tab	1 009	26.43	195.17	60.03	196 922.17
	Pantoprazole 40mg	Tab	2 803	73.43	347.93	101.02	975 253.68
	Pantoprazole	Inj	5	0.13	176.63	6.73	883.16

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of pantoprazole containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.28 shows that the average cost of pantoprazole injections revealed a practical significant decrease ($d > 0.8$) from 2001 to 2005 ($d = 1.99$) and from 2001 to 2006 ($d = 15.31$) (refer to section 4.7.3.4).

Rabeprazole

Appendix B shows that the prevalence of Pariet® 10mg tablets was the highest during 2002 ($n = 2\,864$). Pariet® 10mg tablets had the highest average cost ($R292.91 \pm 85.78$) during 2006. The prevalence of Pariet® 20mg tablets was the highest ($n = 4\,848$) during 2006 and had the highest average cost ($R468.90 \pm 154.24$) during 2006 (Appendix B).

Table 5.29 provides a summary of medicine items, containing rabeprazole as active ingredient, with CPI > 1 (refer to section 4.6.4).

Table 5.29: Summary of medicine items, containing rabeprazole as active ingredient, with CPI > 1 for the 2001, 2002, 2004, 2005 and 2006 (extracted Appendix B).

Product	DF	2001	2002	2004	2005	2006
Pariet® 10mg ^I	Tab	1.02	1.18	1.10	1.36	1.67
Pariet® 20mg ^I	Tab	1.39	1.57	1.83	2.33	2.67

DF – Dosage form

I – Innovator medicine item

G – Generic medicine item

Table 5.29 shows that Pariet® 10mg and Pariet® 20mg had a CPI greater than one for the five study years. Therefore it might be assumed that Pariet® 10mg and Pariet® 20mg therapy was relatively expensive during the five study years (refer to section 4.7.3.4)

Table 5.30 provides an overview of the prevalence, average cost and total cost of medicine items, containing rabeprazole as active ingredient, for the five study years.

Table 5.30: The prevalence, average cost and total cost of medicine items, containing rabeprazole as active ingredient, for the 2001, 2002, 2004, 2005 and 2006.

Year	Active ingredient	DF	Prevalence	Prevalence %	Average cost per medicine item (R)	Std Dev ±	Total cost (R)
2001	Rabeprazole 10mg	Tab	2 231	100.00	233.52	64.28	520 978.63
	Rabeprazole 20mg	Tab	3 703	100.00	318.70	133.45	1 180 139.47
2002	Rabeprazole 10mg	Tab	2 864	100.00	288.25	72.54	825 553.31
	Rabeprazole 20mg	Tab	4 401	100.00	381.87	161.92	1 680 621.53
2004	Rabeprazole 10mg	Tab	2 113	100.00	227.18	71.07	480 035.50
	Rabeprazole 20mg	Tab	4 848	100.00	376.51	159.37	1 825 301.88
2005	Rabeprazole 10mg	Tab	1 006	100.00	246.65	75.46	248 130.57
	Rabeprazole 20mg	Tab	4 073	100.00	422.63	172.19	1 721 376.37
2006	Rabeprazole 10mg	Tab	416	100.00	292.91	85.78	121 850.73
	Rabeprazole 20mg	Tab	2 789	100.00	468.90	154.24	1 307 772.69

DF – Dosage form

% - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of rabeprazole containing medicine items claimed for the corresponding year multiplied by hundred.

Table 5.30 shows that the average cost of rabeprazole 20mg tablets revealed a practical significant increase ($d > 0.8$) from 2001 to 2006 ($d = 0.973$) (refer to section 4.7.3.4).

Summary

Table 5.31 provides a summary of the top five PPIs, according to cost, over the study period.

Table 5.31: Summary of the top five PPIs, according to cost, for 2001, 2002, 2004, 2005 and 2006 (extracted from appendix D).

Position	2001		2002		2004		2005		2006	
	Product	CPI	Products	CPI	Product	CPI	Product	CPI	Product	CPI
1	Lanzor® 30mg ^I	1.11	Lanzor® 30mg ^I	1.20	Lanzor® 30mg ^I	1.24	Lanzor® 30mg ^I	1.58	Pariet® 20mg ^I	1.94
2	Losec mups® 20mg ^I	1.15	Losec mups® 20mg ^I	1.18	Nexiam® 40mg ^I	1.06	Nexiam® 40mg ^I	1.26	Nexiam® 40mg ^I	1.78
3	Lanzor® 15mg ^I	0.80	Lanzor® 15mg ^I	0.88	Losec mups® 20mg ^I	1.34	Pariet® 20mg ^I	1.61	Adco-omeprazole® 20mg ^G	0.64
4	Pantoloc® 40mg ^I	1.09	Pariet® 20mg ^I	1.03	Nexiam® 20mg ^I	0.77	Controloc® 40mg ^I	1.37	Sandoz-omeprazole® 20mg ^G	0.63
5	Pariet® 20mg ^I	0.89	Nexiam® 40mg ^I	0.99	Lanzor® 15mg ^I	0.90	Nexiam® 20mg ^I	0.89	Altosec® 20mg ^G	0.59

I – Innovator medicine item

G – Generic medicine item

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.31 shows that the top five PPI products, according to cost, stayed reasonably the same from 2001 to 2006. Lanzor® 30mg capsules remained the PPI with the highest cost from 2001 to 2005. During 2006 Pariet® 20mg tablets were the PPI with the highest cost. Lanzor® 15mg capsules and Losec mups® 20mg were only among the five PPIs with the highest cost from 2001 to 2004. Pantoloc® 40 mg appeared among the top five PPIs during 2001. All the PPI products among the top five were innovator medicine items from 2001 to 2005. Three out of the five products were generic medicine items during 2006 namely Adco-omeprazole® 20mg, Sandoz-omeprazole® 20mg and Altosec® 20mg.

Tables 5.11; 5.13, 5.15; 5.17; 5.21; 5.23; 5.25; 5.26; 5.28; and 5.30 revealed the relatively large standard deviations that were encountered with the average cost. This was an indication that various quantities of the acid reducing medicine were prescribed, an aspect that is important in calculating “daily treatment cost”. This aspect is being addressed in section 5.8.2.

5.6 COMPARISON OF INNOVATOR AND GENERIC MEDICINE ITEMS AS RELATED TO PREVALENCE AND COST

In the following section an overview was given of the prescribing patterns of innovator and generic medicine items.

5.6.1 OVERVIEW OF INNOVATOR AND GENERIC MEDICINE ITEMS

Table 5.32 provides an overview of innovator and generic medicine items of the total database, GIT and acid reducers for the five study years.

Table 5.32: Overview of innovator and generic medicine items on the total database for the years 2001, 2002, 2004, 2005 and 2006.

	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per item (R)	Std dev ±	Total cost (R)	Cost %
T o t a l d a t a b a s e	2001	Innovator	2 160 778	73.22	151.10	167.84	326 405 166.00	85.96
		Generic	790 548	26.78	67.24	63.70	53 303 323.23	14.04
		TOTAL	2 951 326	100.00			379 708 489.23	100.00
	2002	Innovator	2 896 367	77.65	177.13	231.74	512 466 999.00	85.22
		Generic	1 145 778	28.35	76.61	73.62	88 883 325.65	14.78
		TOTAL	4 042 145	106.00			601 350 324.65	100.00
	2004	Innovator	3 525 420	66.44	155.80	270.06	549 258 574.00	83.07
		Generic	1 780 426	33.56	62.88	74.30	111 962 426.00	16.93
		TOTAL	5 305 846	100.00			661 221 000.00	100.00
	2005	Innovator	2 330 073	64.60	143.24	272.22	333 766 178.00	82.24
		Generic	1 276 919	35.40	56.43	73.87	72 062 918.99	17.76
		TOTAL	3 606 992	100.00			405 829 096.99	100.00
	2006	Innovator	1 416 058	59.73	152.02	294.67	215 271 485.00	77.11
		Generic	954 511	40.27	66.93	85.48	63 889 172.58	22.89
		TOTAL	2 370 569	100.00			279 160 657.58	100.00
G I T	2001	Innovator	140 680	78.35	177.00	197.84	24 900 576.99	88.42
		Generic	38 876	21.65	83.88	86.64	3 261 102.10	11.58
		TOTAL	179 556	100.00			28 161 679.09	100.00
	2002	Innovator	168 787	73.68	197.44	206.29	33 325 481.66	84.64
		Generic	60 306	26.32	100.28	101.08	6 047 454.64	15.36
		TOTAL	229 093	100.00			39 372 936.30	100.00
	2004	Innovator	213 904	72.33	185.23	418.45	39 620 540.52	89.55
		Generic	81 834	27.67	56.52	63.63	4 625 419.50	10.45
		TOTAL	295 738	100.00			44 245 960.02	100.00
	2005	Innovator	134 825	64.96	172.44	239.31	23 249 217.23	84.90
		Generic	72 732	35.04	56.86	62.71	4 135 559.97	15.10
		TOTAL	207 557	100.00			27 384 777.20	100.00
	2006	Innovator	77 611	56.05	163.38	181.02	12 679 837.00	73.29
		Generic	60 847	43.95	75.94	80.58	4 620 725.83	26.71
		TOTAL	138 458	100.00			17 300 562.83	100.00

Table 5.32 (Continued): Overview of innovator and generic medicine items on the total database for the years 2001, 2002, 2004, 2005 and 2006.

	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per item (R)	Std dev ±	Total cost (R)	Cost %
A c c i d e n t i f i c a t i o n s	2001	Innovator	69 104	85.55	243.00	182.20	16 792 609.69	90.38
		Generic	11 669	14.45	153.25	107.90	1 788 242.25	9.62
		TOTAL	80 773	100.00			18 580 851.94	100.00
	2002	Innovator	87 240	81.05	260.60	192.10	22 734 717.53	86.66
		Generic	20 397	18.95	171.51	121.41	3 498 261.28	13.34
		TOTAL	107 637	100.00			26 232 978.81	100.00
	2004	Innovator	111 104	82.06	235.21	182.98	26 132 932.68	93.61
		Generic	24 297	17.94	73.48	69.40	1 785 272.12	6.39
		TOTAL	135 401	100.00			2 791 8204.80	100.00
	2005	Innovator	63 312	68.40	231.37	184.11	14 648 430.17	86.70
		Generic	29 253	31.60	65.58	76.79	2 246 343.08	13.30
		TOTAL	92 565	100.00			16 894 773.25	100.00
	2006	Innovator	30 171	51.00	238.56	207.58	7 197 568.82	69.25
		Generic	28 986	49.00	110.27	86.18	3 196 163.34	30.75
		TOTAL	59 157	100.00			10 393 732.16	100.00

Prevalence % - The total number of innovator or generic medicine items claimed for the specific period (year) divided by the total number of medicine items claimed for the corresponding year multiplied by hundred.

5.6.1.1 PREVALENCE OF INNOVATOR/GENERIC MEDICINE ITEMS ON THE TOTAL DATABASE

In the following section an overview will be given of the prevalence of innovator and generic medicine items on the total database, GIT and acid reducing medicine items.

Prevalence according to innovator and generic medicine items on the total database

Figure 5.3 illustrates the changes in the prevalence percentage for innovator and generic medicine items of the total database from 2001 to 2006.

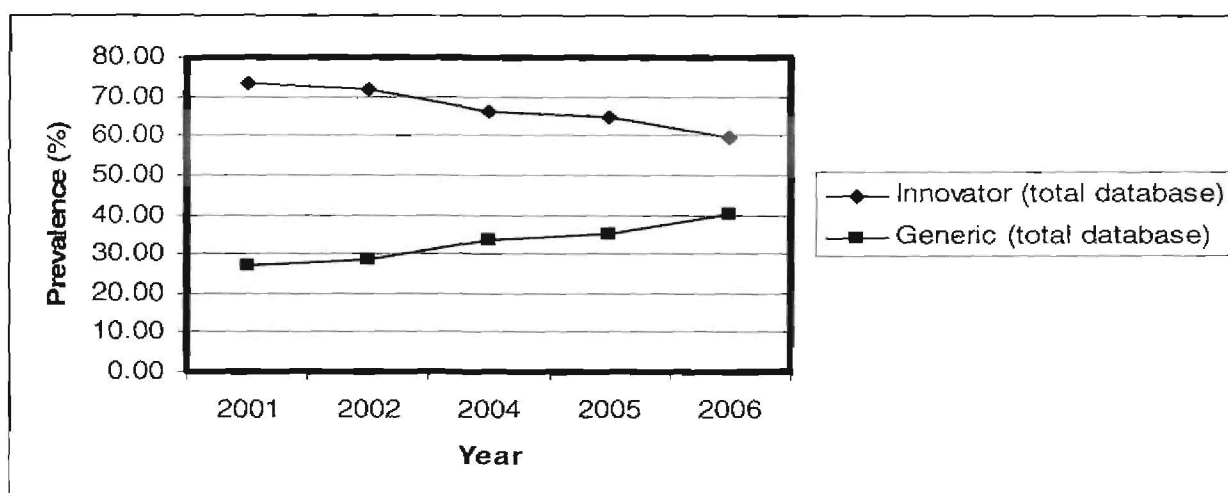


Figure 5.3: The prevalence percentage of innovator and generic medicine items on the total database for 2001, 2002, 2004, 2005 and 2006.

There was a steady decrease in the percentage innovator medicine items claimed through this medicine claims database; from 2001 to 2006 there was a 13.49% decrease in the percentage innovator medicine items claimed. In contrast, there was gradual increase in the percentage generic medicine items claimed (refer to figure 5.3 and table 5.32).

Prevalence according to innovator and generic GIT medicine items

Figure 5.4 shows an illustration of the prevalence percentage for innovator and generic GIT medicine items for the five study years.

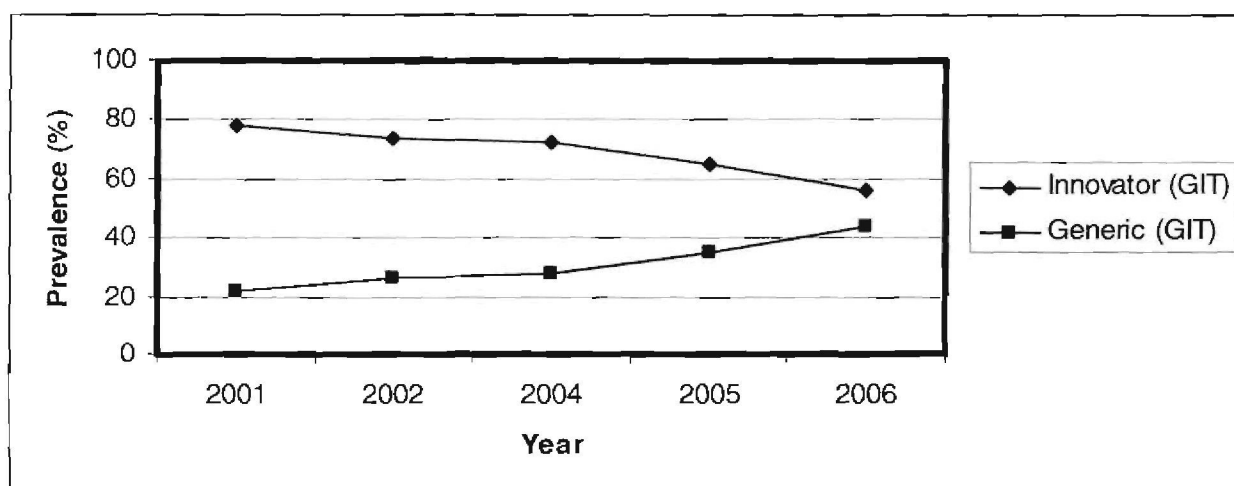


Figure 5.4: The prevalence percentage of innovator and generic GIT medicine items for 2001, 2002, 2004, 2005 and 2006.

The results reveal a steady decrease (total decrease of 22.30%) in the percentage innovator medicine items claimed from 2001 to 2006. There was, however, a gradual increase in the percentage generic medicine items claimed from 21.65% ($n = 38\,876$) in 2001 to 43.95% ($n = 60\,847$) in 2006 (refer to figure 5.4 and table 5.32).

Prevalence according to innovator and generic acid reducing medicine items

Figure 5.5 illustrates the prevalence percentage of innovator and generic acid reducing medicine items for the five study years.

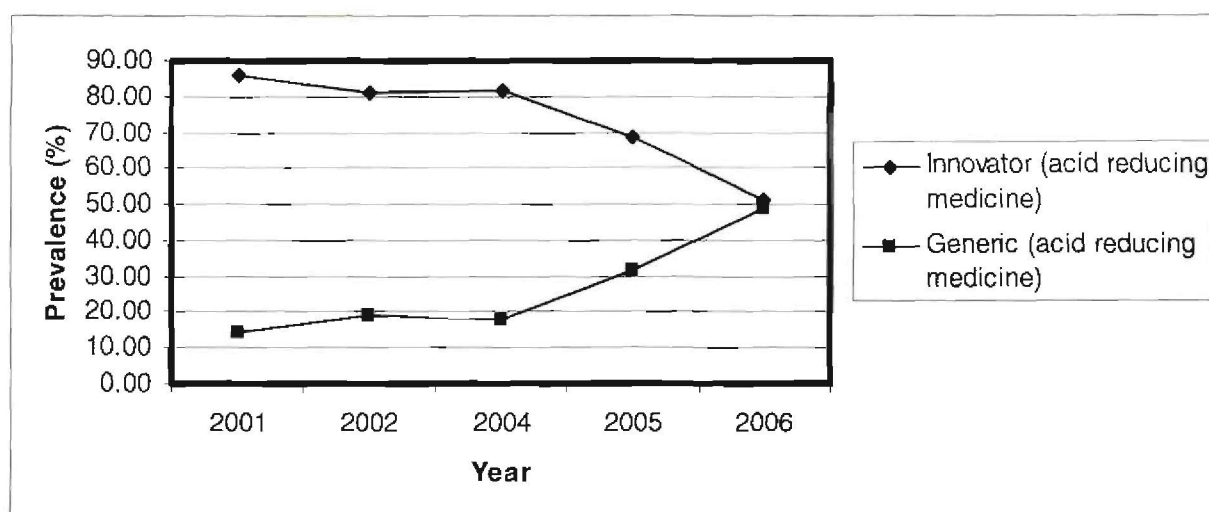


Figure 5.5: The prevalence percentage of innovator and generic acid reducing medicine for 2001, 2002, 2004, 2005 and 2006.

From 2001 to 2002 there was a 4.50% decrease in the percentage innovator medicine items claimed. There was a 1.01% increase in the percentage innovator medicine items claimed from 2002 to 2004. A reduction of 13.66% from 2004 to 2005 and 17.40% from 2005 to 2006 in the percentage innovator medicine items claimed can be observed (refer to figure 5.5 and table 5.32).

Summary

There was a steady decrease in the percentage innovator medicine items claimed for the five study years. In turn there was a gradual increase in the percentage generic medicine items claimed. This trend is true for both the medicine items claimed on the total database and for GIT medicine items. In the case of acid reducing medicine there was an initial decrease, followed by a slight increase and a decrease in the percentage innovator medicine items claimed. In turn there was an increase followed by a decrease and a final increase in the percentage generic medicine items claimed.

Possible explanations for the increase in generic utilisation include the following:

- The introduction of more generic alternatives to the South African market in comparison with a very low rate of introduction of new chemical entities.
- The wider implementation of generic reference pricing, including the implementation of more stringent generic reference pricing models.

- The introduction of various formularies that promote generic utilisation for the management of disease conditions, including the chronic disease list (CDL) and Prescribed Minimum Benefits (PMB) in 2004 (refer to section 3.5.2).
- Greater awareness of the availability and use of generics by patients and providers.
- Mandatory generic substitution at pharmacy level (Bester & Hammann, 2005:15; Bester *et al.*, 2006:7).

5.6.1.2 AVERAGE COST OF INNOVATOR/GENERIC MEDICINE ITEMS

Table 5.32.1 provides an overview of the average cost of innovator and generic medicine items claimed during the study years.

Table 5.32.1: The average cost of innovator and generic medicine items claimed for 2001, 2002, 2004, 2005 and 2006.

Year	Total database		GIT		Acid reducers	
	Innovator	Generic	Innovator	Generic	Innovator	Generic
2001	R151.10±167.84	R67.24±63.70	R177.00±197.84	R83.88±86.64	R243.00±182.20	R153.25±107.90
2002	R177.13±231.74	R76.61±73.62	R197.44±206.29	R100.28±101.08	R260.60±192.10	R171.51±121.41
2004	R155.80±270.06	R62.88±74.30	R185.23±418.45	R56.52±63.63	R235.21±182.98	R73.48±69.40
2005	R143.24±272.22	R56.43±73.87	R172.44±239.31	R56.86±62.71	R231.37±184.11	R65.58±76.79
2006	R152.02±294.67	R66.93±85.48	R163.38±181.02	R75.94±80.58	R238.56±207.58	R110.27±86.18

The average cost of innovator and generic medicine items claimed increased from 2001 to 2002, decreased from 2002 to 2005 and then increased again from 2005 to 2006. This trend was true for all medicine items on the total database as well as for acid reducers (table 5.32.1).

The average cost of innovator GIT medicine items claimed increased from 2001 to 2002 and decreased from 2002 to 2006. The average cost of generic GIT medicine items claimed increased from 2001 to 2002, decreased from 2002 to 2005 and then increased again from 2005 to 2006 (the same as the total database and acid reducers) (table 5.32.1).

The average cost between generic acid reducing medicine items decreased with practical significance ($d = 0.81$) from 2001 to 2005 (refer to section 4.7.3.4).

5.6.1.3 TOTAL COST OF INNOVATOR AND GENERIC ITEMS

Table 5.32.2 provides an overview of the cost percentage of innovator and generic medicine items claimed during the study period.

Table 5.32.2: The cost percentage of innovator and generic medicine items claimed on the total database, GIT medicine items and acid reducers for 2001, 2002, 2004, 2005 and 2006.

Year	Total database		GIT		Acid reducers	
	Innovator	Generic	Innovator	Generic	Innovator	Generic
2001	85.96%	14.04%	88.42%	11.58%	90.38%	9.62%
	(n = R326 405 166)	(n = R53 303 323.23)	(n = R24 900 576.99)	(n = R3 261 102.10)	(n = R16 792 609.69)	(n = R1 788 242.25)
2002	85.22%	14.78%	84.64%	15.36%	86.66%	13.34%
	(n = R512 466 999)	(n = R88 883 325.65)	(n = R33 325 481.66)	(n = R6 047 454.64)	(n = R22 734 717.53)	(n = R3 498 261.28)
2004	83.07%	16.93%	89.55%	10.45%	93.61%	6.39%
	(n = R549 258 574)	(n = R111 962 426.00)	(n = R39 620 540.52)	(n = R4 625 419.50)	(n = R26 132 932.68)	(n = R1 785 272.12)
2005	82.24%	17.76%	84.90%	15.10%	86.70%	13.30%
	(n = R333 766 178)	(n = R72 062 918.99)	(n = R23 249 217.23)	(n = R4 135 559.97)	(n = R14 648 430.17)	(n = R2 246 343.08)
2006	77.11%	22.89%	73.29%	26.71%	69.25%	30.75%
	(n = R21 5271 485)	(n = R63 889 172.58)	(n = R1 2679 837.00)	(n = R4 620 725.83)	(n = R3 196 163.34)	(n = R3 196 163.34)

% - The cost of generic or innovator medicine items claimed for the specific period (year) divided by the total cost (sum of generic and innovator medicine items claimed) for the corresponding year multiplied by hundred.

The percentage which innovator medicine items claimed contributed to the total cost, decreased from 2001 to 2006 (table 5.32.2).

The percentage which GIT and acid reducing innovator medicine items contributed to the total cost, decreased from 2001 to 2002, increased from 2002 to 2004 and again decreased from 2004 to 2006 (table 5.32.2). The percentage acid reducer innovators decreased from 2001 to 2002, increased from 2002 to 2004 and decreased from 2004 to 2006 (refer to section 5.6.1.1). The increase from 2002 to 2004 might be explained by the introduction of esomeprazole (Nexiam®) into the market during 2002 (refer to section 5.5.3.2).

5.6.2 PREVALENCE ACCORDING TO INNOVATOR AND GENERIC FOR SUB-PHARMACOLOGICAL GROUPS

In the following section an in-depth study will be done on the prevalence of the different sub-pharmacological groups of acid reducing medicine according to innovator and generic medicine claimed.

Figure 5.6 shows an illustration of the prevalence percentage for innovator and generic medicine according to the sub-pharmacological groups of acid reducing medicine for the five study years.

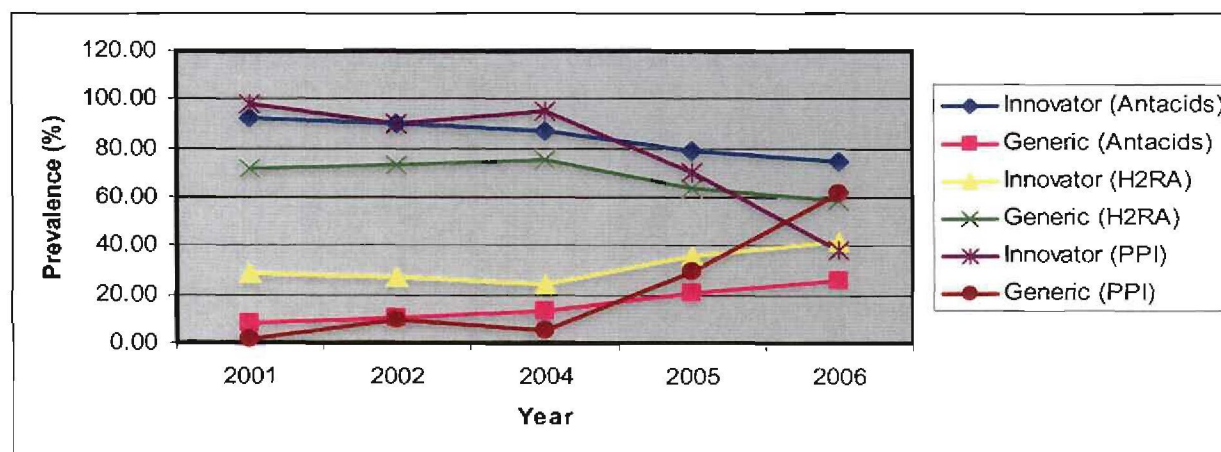


Figure 5.6: Prevalence percentage for the sub-pharmacological groups of acid reducing medicine for 2001, 2002, 2004, 2005 and 2006.

As revealed in Figure 5.6 there was a steady decrease in the percentage innovator antacids claimed. In turn there was gradual increase in the percentage generic antacids claimed (refer to appendix E). New legislation on generic medicine came into effect during 2003. This compelled the pharmacist to inform all patients of the benefits of generic substitution. This decrease might be the result of the implementation of generic substitution (refer to section 3.5.1).

From 2001 to 2004 there was a steady increase in the percentage generic H₂RAs claimed. The percentage generic H₂RAs claimed increased from 71.65 % (n = 9 033) in 2001 (N = 12 606) to 72.84 % (n = 11 761) in 2002 (N = 16 147) and to 75.64 % (n = 15 780) in 2004 (N = 20 861). From 2004 to 2006 there was a decrease in the percentage generic H₂RAs claimed. The percentage generic H₂RAs claimed decreased from 63.87 % (n = 9 745) in 2005 (N = 15 257) to 58.25 % (n = 6 291) in 2006 (N = 10 800) (figure 5.6).

A possible explanation for this trend may be the implementation of the new pricing regulation in 2004 (refer to section 3.5.3). Since there is a small price difference between the innovator and generic (due to the new pricing regulator) the patient rather takes the innovator. Since there were no generic medicine items of Zantac[®] effervescent tablets (150mg and 300mg) available and these products were often prescribed during the study years, it might be another explanation (refer to section 5.5.3.1).

The percentage generic PPIs claimed increased from 1.69 % (n = 671) in 2001 (N = 39 730) to 9.84 % (n = 5351) in 2002 (N = 54 369). The percentage generic PPIs claimed decreased with 4.91 % from 2002 to 2004 only to increase again from 2004 to 2006. The percentage generic PPIs claimed increased from 4.93 % (n = 3 512) in 2004 (N = 71 279) to 61.18 % (n = 18 670) in 2006 (N = 30 517) (figure 5.6). This decrease observed in the percentage generic PPIs claimed from 2002 to 2004, might be explained by the introduction of Nexiam[®] (esomeprazole) into the market during 2002. The drastic increase in the percentage generic innovator PPIs from 2004 to 2006 might be explained by an increase of the availability of a number of generic medicine items (refer to section 5.6.3.2).

Since all the cytoprotective agents claimed for the study years 2001, 2002, 2004 and 2005 were innovators; they are not included in figure 5.6.

5.6.3 PREVALENCE AND COST ACCORDING TO INNOVATOR/GENERIC FOR ACTIVE INGREDIENTS

In the following section an in-depth study will be done of the prevalence, average cost and total cost of acid reducing medicine items with special reference to H₂RAs and PPIs according to innovator and generic medicine per active ingredient claimed.

5.6.3.1 PREVALENCE AND COST OF INNOVATOR AND GENERIC ACTIVE INGREDIENTS OF H₂RAs

Table 5.33 provides an overview of the prevalence, average cost and total cost of the active ingredients of H₂RAs for the five study years.

Table 5.33: Prevalence and cost of the active ingredients of H₂RAs of innovator and generic medicine items.

Active ingredient	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per medicine (R)	Std dev ±	Total cost (R)
Cimetidine	2001	Innovator	71	1.53	300.40	258.11	21 328.58
		Generic	4 575	98.47	155.34	90.66	710 705.25
		TOTAL	4 646	100.00			732 033.83
	2002	Innovator	36	0.68	220.81	130.62	7 949.12
		Generic	5 281	99.32	148.09	95.10	782 068.15
		TOTAL	5 317	100.00			790 017.27
	2004	Innovator	35	0.66	188.23	203.88	6 588.10
		Generic	5 257	99.34	67.75	75.10	356 182.73
		TOTAL	5 292	100.00			362 770.83
	2005	Innovator	23	0.92	113.40	199.54	2 608.23
		Generic	2 482	99.08	27.25	16.86	67 625.41
		TOTAL	2 505	100.00			70 233.64
	2006	Innovator	3	0.28	340.64	276.44	1 021.92
		Generic	1 050	99.72	29.83	17.74	31 323.41
		TOTAL	1 053	100.00			32 345.33
Famotidine	2001	Innovator	84	100.00	437.14	232.36	36 719.79
	2002	Innovator	71	100.00	441.28	367.40	31 331.11
	2004	Innovator	107	100.00	484.60	100.72	51 851.67
Nizatidine	2001	Innovator	45	100.00	243.82	209.52	10 971.91
	2002	Innovator	183	100.00	208.71	153.77	45 416.38
	2004	Innovator	233	100.00	221.78	134.62	51 674.85
	2005	Innovator	174	100.00	174.67	94.60	30 392.10
	2006	Innovator	95	100.00	120.87	41.63	11 482.47

Table 5.33 (Continued): Prevalence and cost of the active ingredients of H₂RAs of innovator and generic medicine items.

Active ingredient	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per medicine (R)	Std dev ±	Total cost (R)
Ranitidine	2001	Innovator	3 373	43.07	176.59	125.10	595 626.25
		Generic	4 458	56.73	180.58	98.09	805 023.43
		TOTAL	7 831	99.8			1 400 649.68
	2002	Innovator	4 063	38.54	208.71	153.77	847 991.68
		Generic	6 480	61.46	157.68	86.76	1 021 755.44
		TOTAL	10 543	100.00			1 869 747.12
	2004	Innovator	4 706	30.90	288.49	209.60	1 357 647.16
		Generic	10 523	69.10	83.61	68.34	879 859.91
		TOTAL	15 229	100.00			2 237 507.07
	2005	Innovator	5 314	42.25	319.79	213.46	1 699 709.53
		Generic	7 263	57.75	48.87	29.01	354 915.16
		TOTAL	12 577	100.00			2 054 624.69
	2006	Innovator	4 411	45.70	310.84	202.09	1 371 125.77
		Generic	5 241	54.30	56.18	35.73	29 442.02
		TOTAL	9 652	100.00			1 400 567.79
Ranitidine bismuth citrate	2002	Innovator	33	100.00	288.23	82.04	9 511.46

% - The number of a specific medicine items claimed for the specific period (year) divided by the total number of medicine items claimed for the corresponding year multiplied by hundred.

Since there were no generic medicines available for the famotidine (Pepsid®), nizatidine (Antazid®) and ranitidine bismuth citrate (Pylorid®) over the five study years, the prevalence, average cost and total cost of these medicine items will not be discussed in this section (refer to section 5.5.3). However, these medicine items were included in the relevant tables for completeness.

Prevalence of innovator and generic medicine items according to the active ingredients of H₂RAs

Table 5.33.1 provides the prevalence percentage for innovator and generic medicine items claimed of the active ingredient of H₂RAs for the five study years.

Table 5.33.1 : The prevalence percentage for innovator and generic medicine items of the active ingredients of H₂RAs

Year	Cimetidine		Famotidine		Nizatidine		Ranitidine		Ranitidine bismuth citrate	
	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
2001	1.53%	98.47%	100.00%	0.00%	100.00%	0.00%	43.07%	56.73%	0*	0*
	(n = 71)	(n = 4 575)	(n = 84)		(n = 45)		(n = 3 373)	(n = 4 458)		
2002	0.68%	99.32%	100.00%	0.00%	100.00%	0.00%	38.54%	61.46%	100.00%	0*
	(n = 36)	(n = 5 281)	(n = 71)		(n = 183)		(n = 4 063)	(n = 6 480)	(n = 33)	
2004	0.66%	99.34%	100.00%	0.00%	100.00%	0.00%	30.90%	69.10%	0*	0*
	(n = 35)	(n = 5 257)	(n = 107)		(n = 233)		(n = 4 706)	(n = 10 523)		
2005	0.92%	99.08%	0*	0*	100.00%	0.00%	42.25%	57.75%	0*	0*
	(n = 23)	(n = 2 482)			(n = 174)		(n = 5 314)	(n = 7 263)		
2006	0.28%	99.72%	0*	0*	100.00%	0.00%	45.70%	54.30%	0*	0*
	(n = 3)	(n = 1 050)			(n = 95)		(n = 4 411)	(n = 5 241)		

% - The prevalence of generic or innovator medicine items claimed for the specific period (year) divided by the total prevalence (sum of generic and innovator medicine items claimed) for the corresponding year multiplied by hundred.

* - Indicates that that specific active ingredient was not present on the Interpharm Data systems® for the corresponding year.

Table 5.33.1 shows that the prevalence percentage of cimetidine containing generic medicine items increased from 2001 to 2004; decreased from 2004 to 2005 and increased again from 2005 to 2006. The increase in the percentage generic medicine items claimed from 2002 to 2004 may be the result of the new legislation on generic medicine, which came into effect on 2 May 2003 (refer to section 3.5.1). The decrease in the percentage generic medicine items from 2004 and 2005 may be due to the small price difference (R86.15) between innovator and generic medicine items in 2005 (table 5.) or the 52.66% decrease in the number of cimetidine medicine items from 2004 to 2005 (refer section 5.5.3). The cimetidine containing innovator medicine items, represented less than 2% of all cimetidine medicine items claimed during all the study years.

The prevalence percentage of ranitidine containing generic medicine items claimed, increased from 2001 to 2004. It is expected that there should be a continuous increase in the percentage generic medicine items claimed due to the implementation of the new generic legislation (refer to section 3.5.1). The percentage ranitidine containing generic medicine items, however, decreased from 2004 to 2006 (table 5.33.1). A possible explanation for the decrease in the prevalence percentage of ranitidine containing generic medicine items might be that the pharmacists neglected to inform the patient of the benefit of generic substitution. The pharmacist might feel that the profit is better on the innovator medicine item since it is more expensive (refer to section 3.5.3 in regard to the single exit price).

Average cost of innovator and generic medicine items according to the active ingredients of H₂RAs

Table 5.33.2 provides the average cost for innovator and generic medicine items claimed of the active ingredients of H₂RAs for the five study years.

Table 5.33.2: The average cost for innovator and generic medicine items of the active ingredient of H₂RAs

Year	Cimetidine		Famotidine	Nizatidine	Ranitidine		Ranitidine bismuth citrate
	Innovator	Generic	Innovator	Innovator	Innovator	Generic	Innovator
2001	R300.40±258.11	R155.34±90.66	R437.14±232.36	R243.82±209.52	R176.59±125.10	R180.58±98.09	0*
2002	R220.81±130.62	R148.09±95.10	R441.28±367.40	R208.71±153.77	R208.71±153.77	R157.68±86.76	R288.23±82.04
2004	R188.23±203.88	R67.75±75.10	R484.60±100.72	R221.78±134.62	R288.49±209.60	R83.61±68.34	0*
2005	R113.40±199.54	R27.25±16.86	0*	R174.67±94.60	R319.79±213.46	R48.87±29.01	0*
2006	R340.64±276.44	R29.83±17.74	0*	R120.87±41.63	R310.84±202.09	R56.18±35.73	0*

* - Indicates that that specific active ingredient was not present on the Interpharm Data systems® for the corresponding year.

Table 5.33.2 shows that the average cost per cimetidine containing innovator and generic medicine item claimed, decreased from 2001 to 2005. The average cost per cimetidine containing innovator medicine item claimed, increased from 2005 to 2006. While the average cost per cimetidine containing generic medicine item claimed, decreased from 2005 to 2006.

The average cost between cimetidine containing generic medicine items decreased with practical significance from 2001 to 2004 ($d = 0.96$), from 2001 to 2005 ($d = 1.41$), from 2001 to 2006 ($d = 1.38$) and from 2004 to 2005 ($d = 1.26$) (refer to section 4.7.3.4). There was a practical significant difference ($d = 1.12$) between the average cost of cimetidine containing innovator and generic medicine items during 2006 (refer to section 4.7.3.4).

The average cost per ranitidine containing innovator medicine item claimed, increased from 2001 to 2005 and decreased from 2005 to 2006. While the average cost per ranitidine containing generic medicine item claimed, decreased from 2001 to 2005 and increased from 2005 to 2006 (table 5.33.2).

The average cost between ranitidine containing generic medicine items decreased with practical significance from 2001 to 2004 ($d = 0.99$), from 2001 to 2005 ($d = 1.34$) and from 2001 to 2006 ($d = 1.27$) (refer to section 4.7.3.4). There was a practical significant difference between the average cost of ranitidine containing innovator and generic medicine items during 2004 ($d = 0.98$), 2005 ($d = 1.27$) and 2006 ($d = 1.26$) (refer to section 4.7.3.4).

Total cost of innovator and generic medicine items according to the active ingredient of H₂RAs

Table 5.33.3 provides the total cost for innovator and generic medicine items claimed of the active ingredients of H₂RAs for the five study years.

Table 5.33.3: The total cost of innovator and generic medicine items of the active ingredients of H₂RAs

Year	Cimetidine		Famotidine	Nizatidine	Ranitidine		Ranitidine bismuth citrate
	Innovator	Generic	Innovator	Innovator	Innovator	Generic	Innovator
2001	2.91% (n = R21 328.58)	97.09% (n = R710 705.25)	100% (n = R36 719.79)	100.00% (n = R1 0971.91)	42.52% (n = R595 626.25)	57.48% (n = R805 023.43)	0*
2002	1.01% (n = R79 49.12)	98.99% (n = R782 068.15)	100% (n = R31 331.11)	100.00% (n = R45 416.38)	45.35% (n = R847 991.68)	54.65% (n = R1 021 755.44)	100.00% (n = R9 511.46)
2004	1.82% (n = R6 588.10)	98.18% (n = R356 182.73)	100% (n = R51 851.67)	100.00% (n = R51 674.85)	60.68% (n = R1 357 647.16)	39.32% (n = R879 859.91)	0*
2005	3.71% (n = R2 608.23)	96.29% (n = R676 25.41)	0*	100.00% (n = R30 392.10)	82.73% (n = R1 699 709.53)	17.27% (n = 354 915.16)	0*
2006	3.16% (n = 1 021.92)	96.84% (n = R313 23.41)	0*	100.00% (n = R11 482.47)	97.89% (n = R1 371 125.77)	2.10% (n = R29 442.02)	0*

% - The cost of generic or innovator medicine items claimed for the specific period (year) divided by the total cost (sum of generic and innovator medicine items claimed) for the corresponding year multiplied by hundred.

* - Indicates that that specific active ingredient was not present on the Interpharm Data systems® for the corresponding year.

Table 5.33.3 shows that the cost percentage of innovator cimetidine containing medicine items decreased from 2001 to 2002, increased from 2002 to 2005 and then decreased from 2005 to 2006. The cost percentage ranitidine containing innovator medicine items represented as part of the total cost of ranitidine medicine items increased continuously from 2001 to 2006.

5.6.3.2 PREVALENCE AND COST OF INNOVATOR AND GENERIC MEDICINE ITEMS ACCORDING TO THE ACTIVE INGREDIENTS OF PPIs

Table 5.34 gives an overview of the prevalence, average cost and total cost of the active ingredients of PPIs for the five study years.

Table 5.34: An overview of the prevalence, average cost and total cost of innovator and generic medicine items active ingredients of PPIs.

Active ingredient	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per medicine (R)	Std dev ±	Total cost (R)
Omeprazole/ amoxicillin/ clarithromycin	2001	Innovator	266	100.00	678.84	121.37	180 572.15
	2002	Innovator	278	100.00	740.31	99.83	205 806.22
	2004	Innovator	46	100.00	676.80	194.10	31 132.77
	2005	Innovator	2	100.00	609.90	0.00	1 219.80
Esomeprazole	2002	Innovator	5 984	100.00	339.85	149.17	2 033 663.86
	2004	Innovator	19 332	100.00	288.96	137.42	5 586 163.08
	2005	Innovator	10 532	100.00	288.70	133.45	3 040 576.85
	2006	Innovator	4 274	100.00	383.38	133.99	1 638 553.71
Lansoprazole	2001	Innovator	14 855	100.00	359.90	141.32	5 346 346.95
	2002	Innovator	16 965	100.00	401.39	147.13	6 809 535.30
	2004	Innovator	17 383	100.00	344.57	150.83	5 989 745.23
		Innovator	7 964	86.91	367.08	155.44	2 923 453.58
		Generic	1 199	13.09	129.29	78.21	155 017.85
	2005	TOTAL	9 163	100.00			3 078 471.43
		Innovator	1 021	18.86	362.41	195.55	370 022.05
		Generic	4 392	81.14	103.14	108.48	452 974.80
	2006	TOTAL	5 413	100.00			822 996.85

Table 5.34 (Continued): An overview of the prevalence, average cost and total cost of innovator and generic medicine items active ingredients of PPIs.

Active ingredient	Year	Innovator/ Generic	Prevalence	Prevalence %	Average cost per medicine (R)	Std dev ±	Total cost (R)
Omeprazole	2001	Innovator	12 018	94.71	383.34	157.05	4 606 947.49
		Generic	671	5.29	283.61	152.30	190 301.54
		TOTAL	12 689	100.00			4 797 249.03
	2002	Innovator	10 974	67.22	401.78	175.42	4 409 088.69
		Generic	5 351	32.78	285.29	121.53	1 526 592.01
		TOTAL	16 325	100.00			5 935 680.70
	2004	Innovator	9 779	73.58	397.28	225.00	3 885 036.84
		Generic	3 512	26.42	113.68	74.42	399 258.99
		TOTAL	13 291	100.00			4 284 295.83
	2005	Innovator	2 517	16.11	345.86	259.51	870 086.44
		Generic	13 110	83.89	117.63	69.09	1 542 082.28
		TOTAL	15 627	100.00			2 412 168.72
	2006	Innovator	875	6.34	429.73	423.73	376 015.06
		Generic	12 933	93.66	149.34	45.92	1 931 519.88
		TOTAL	13 808	100.00			2 307 534.94
Pantoprazole	2001	Innovator	5 986	100.00	373.37	137.44	2 234 989.39
	2002	Innovator	7 552	100.00	365.10	142.87	2 757 251.14
	2004	Innovator	14 266	100.00	282.63	136.92	4 032 050.12
	2005	Innovator	8 255	100.00	278.65	118.51	2 300 222.63
		Innovator	2 472	64.76	316.91	121.15	783 398.14
	2006	Generic	1 345	35.24	289.71	97.27	389 660.87
		TOTAL	3 817	100.00			1 173 059.01
Rabeprazole	2001	Innovator	5 934	100.00	286.67	119.87	1 701 118.10
	2002	Innovator	7 265	100.00	344.97	141.59	2 506 174.84
	2004	Innovator	6 961	100.00	331.18	154.71	2 305 337.38
	2005	Innovator	5 079	100.00	387.77	172.70	1 969 506.94
	2006	Innovator	3 205	100.00	446.06	158.60	1 429 623.42

% - The number of medicine items claimed for the specific period (year) divided by the total number of medicine items claimed for the corresponding year multiplied by hundred.

There were no generic medicines available for omeprazole/amoxicillin/clarithromycin (Losec Triple pack®), esomeprazole (Nexiam®) and rabeprazole (Pariet®) over the five study years. For completeness these active ingredients were included in the following tables. The prevalence, average cost and total cost of these medicine items were discussed in section 5.5.3.

Prevalence according to innovator and generic medicine items of the active ingredients of PPIs

Table 5.34.1 provides the prevalence percentage for innovator and generic medicine items claimed of the active ingredients of PPIs for the five study years.

Table 5.34.1: The prevalence percentage for innovator and generic medicine items of the active ingredients of PPIs

Year	Omeprazole /Amoxicillin /Clarithromycin	Esomeprazole	Lansoprazole		Omeprazole		Pantoprazole		Rabeprazole
	Innovator	Innovator	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator
2001	100.00% (n = 266)	0.00%	100.00% (n = 14 855)	0.00%	94.71% (n = 12 018)	5.29% (n = 6 71)	100.00% (n = 5 986)	0.00%	100.00% (n = 5 934)
2002	100.00% (n = 278)	100.00% (n = 5 984)	100.00% (n = 16 965)	0.00%	67.22% (n = 10 974)	32.78% (n = 5 351)	100.00% (n = 7 552)	0.00%	100.00% (n = 7 265)
2004	100.00% (n = 46)	100.00% (n = 19 332)	100.00% (n = 17 383)	0.00%	73.58% (n = 9 779)	26.42% (n = 3 512)	100.00% (n = 14 266)	0.00%	100.00% (n = 6 961)
2005	100.00% (n = 2)	100.00% (n = 10 532)	86.91% (n = 7 964)	13.09% (n = 1 199)	16.11% (n = 2 517)	83.89% (n = 13 110)	100.00% (n = 8 255)	0.00%	100.00% (n = 5 079)
2006	0.00%	100.00% (n = 4 274)	18.86% (n = 1 021)	81.14% (n = 4 392)	6.34% (n = 875)	93.66% (n = 12 933)	64.76% (n = 2 472)	35.24% (n = 1 345)	100.00% (n = 3 205)

% - The prevalence of generic or innovator medicine items claimed for the specific period (year) divided by the total prevalence (sum of generic and innovator medicine items claimed) for the corresponding year multiplied by hundred.

* - Indicates that that specific active ingredient was not present on the Interpharm Data systems® for the corresponding year.

Table 5.34.1 shows that the percentage generic medicine items claimed, increased from 2001 to 2006. This trend is true for lansoprazole and pantoprazole. The increase in the percentage generic medicine items claimed might be a direct result of the implementation of the new generic legislation on 2 May 2003 (refer to section 3.5.1).

With the introduction of generic medicine items for lansoprazole (Lanzor®) in 2005 the percentage innovator medicine items claimed, decreased with 13.09%. From 2005 to 2006 the percentage innovator medicine items claimed, decreased with 68.05% (table 5.34.1).

There were generic medicine items available for pantoprazole (Pantoloc® and Controloc®) in 2006. This caused a decrease of 35.24% in the percentage innovator medicine items claimed (table 5.34.1).

The percentage omeprazole generics claimed increased from 2001 to 2002, decreased 2002 to 2004 and increased again from 2004 to 2006.

Average cost according to innovator and generic medicine items of the active ingredients of PPIs

Table 5.34.2 provides the average cost for innovator and generic medicine items claimed of the active ingredients of PPIs for the five study years.

Table 5.34.2: The average cost for innovator and generic medicine items according to the active ingredients of PPIs

Year	Omeprazole /Amoxicillin/ Clarithromycin	Esomeprazole	Lansoprazole		Omeprazole		Pantoprazole		Rabeprazole
	Innovator	Innovator	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator
2001	R678.00±121.37	0*	R359.90±141.32	0*	R383.34±157.05	R283.61±152.30	R373.37±137.44	0*	R286.67±119.87
2002	R740.31±99.83	R339.85±149.17	R401.39±147.13	0*	R401.78±175.42	R285.29±121.53	R365.10±142.87	0*	R344.97±141.59
2004	R676.80±194.10	R288.96±137.42	R344.57±150.83	0*	R397.28±225.00	R113.68±74.42	R282.63±136.92	0*	R331.18±154.71
2005	R609.90±0.00	R288.70±133.45	R367.08±155.44	R129.29±78.21	R345.86±259.51	R117.63±69.09	R278.65±118.51	0*	R387.77±172.70
2006	0*	R383.38±133.99	R362.41±195.55	R103.14±108.48	R429.73±423.73	R149.34±45.92	R316.91±121.15	R289.71±97.27	R446.06±158.60

* - Indicates that that specific active ingredient was not present on the Interpharm Data systems® for the corresponding year.

Table 5.34.2 illustrates that the average cost per lansoprazole containing innovator medicine items increased from 2001 to 2002 and decreased from 2002 to 2006. The average cost per lansoprazole containing generic medicine items decreased from 2005 to 2006. There was a practical significant difference ($d = 1.33$) between the average cost of lansoprazole containing innovator and generic medicine items during 2006 (refer to section 4.7.3.4).

The average cost per omeprazole containing innovator and generic medicine items increased from 2001 to 2002 (table 5.34.2). The average cost per omeprazole containing generic medicine item decreased with practical significance from 2001 to 2004 ($d = 1.12$), from 2001 to 2005 ($d = 1.10$) and from 2001 to 2006 ($d = 0.88$) (refer to section 4.7.3.4). The decrease in the average cost might be explained by the implementation of the new pricing legislation (refer to section 3.5.3) as well as the increased availability of generic medicine items. There was a practical significant difference between the average cost of omeprazole containing innovator and generic medicine items during 2004 ($d = 1.26$) and 2005 ($d = 0.88$) (refer to section 4.7.3.4).

The average cost per pantoprazole containing innovator medicine item decreased from 2001 to 2005 and increased from 2005 to 2006. The increase from 2005 to 2006 might be explained by the introduction of generic pantoprazole medicine items in 2006. The manufacturer(s) of innovator pantoprazole (Pantoloc® and Controloc®) might have decided to increase the price of Pantoloc® and Controloc® to compensate for the possible loss they would experience because of the availability of the generic product (Topzole®) (table 5.34.2). The difference between the average cost of pantoprazole containing innovator and generic medicine items was of no practical significance ($d = 0.22$) during 2006 (refer to section 4.7.3.4).

The average cost of esomeprazole and rabeprazole innovator medicine items increased from 2005 to 2006. This increase might be due to the fact that the Constitutional Court judgment of 30 September 2005 declared the dispensing fee regulations invalid. The court recommended that the Pricing Committee reconsider the fee of 26% of SEP capped at R26 (refer to section 3.5.3). In this period each pharmacy could charge its own price.

Total cost according to innovator and generic medicine items of the active ingredients of PPIs

Table 5.34.3 provides the total cost for innovator and generic medicine items containing the different PPI active ingredients for the five study years.

Table 5.34.3: The total cost for innovator and generic medicine items according to the active ingredients of PPIs

Year	Omeprazole /Amoxicillin/ Clarithromycin	Esomeprazole	Lansoprazole		Omeprazole		Pantoprazole		Rabeprazole
	Innovator	Innovator	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator
2001	100.00% (n = R180 572.15)	0.00%	100.00% (n = R53 46 346.95)	0.00%	96.03% (n = R4 606 947.49)	3.97% (n = R190 301.54)	100.00% (n = R2 234 989.39)	0.00%	100.00% (n = R1 701 118.10)
2002	100.00% (n = R205 806.22)	100.00% (n = R2 033 663.86)	100.00% (n = R6 809 535.30)	0.00%	74.28% (n = R4 409 088.69)	25.72% (n = R1 526 592.01)	100.00% (n = R2 757 251.14)	0.00%	100.00% (n = R2 506 175.84)
2004	100.00% (n = R31 132.77)	100.00% (n = R5 586 163.08)	100.00% (n = R5 989 745.23)	0.00%	90.68% (n = R3 885 036.84)	9.32% (n = R399 258.99)	100.00% (n = R4 032 050.12)	0.00%	100.00% (n = R2 305 337.38)
2005	100.00% (n = R1 219.80)	100.00% (n = R3 040 576.85)	94.96% (n = R2 923 453.58)	5.04% (n = R155 017.85)	36.07% (n = R870 086.44)	63.93% (n = 1 542 082.28)	100.00% (n = R2 300 222.63)	0.00%	100.00% (n = R1 969 506.94)
2006	0.00%	100.00% (n = R1 638 553.71)	44.96% (n = R370 022.05)	55.04% (n = R452 974.80)	16.30% (n = R376 015.06)	83.70% (n = 193 1519.88)	66.78% (n = R783 398.14)	32.33% (n = R389 660.87)	100.00% (n = R1 429 623.42)

% - The cost of generic or innovator medicine items claimed for the specific period (year) divided by the total cost (sum of generic and innovator medicine items claimed) for the corresponding year multiplied by hundred.

Table.5.34.3 shows the cost percentage that lansoprazole containing innovator medicine items represented of the total cost of lansoprazole for the relevant periods. It decreased from 2004 to 2006 with 55.04%. The decrease was the result of the introduction of lansoprazole generics to the South African market during 2005. The cost percentage that lansoprazole generics contributed to the total cost of lansoprazole containing medicine increased with 50% from 2005 to 2006

The cost percentage that omeprazole containing generic medicine items contributed to the total cost of omeprazole medicine items increased from 2001 to 2002, decreased from 2002 to 2004 and increased again from 2004 to 2006 (table 5.34.3).

Only in 2006 there was a 32.33% decrease in the percentage contribution made by the cost of innovator pantaprazole as part of the total cost for all the medicine items containing pantoprazole (table 5.34.3). This was possibly due to the non-availability of a generic substitution during the previous periods. This aspect needs further monitoring in future studies.

5.7 PREVALENCE AND USAGE PATTERNS OF COMBINATION ACID REDUCING MEDICINES

Combination therapy is necessary in the treatment of *Helicobacter pylori* (*H.pylori*). The literature study (refer to section 2.5.2.6) has shown that *H.pylori* eradication therapy is more effective than antisecretory non-eradication therapy (with or without long-term maintenance antisecretory treatment) in the prevention of recurrent bleeding from a peptic ulcer. It is also found that all patients with peptic ulcer bleeding should be tested for *H.pylori* infection and eradication therapy should be prescribed to *H.pylori* - positive patients.

Prescriptions containing acid reducing medicine on the database were analysed to identify prescriptions containing *H.pylori* eradication therapy. For the purpose of this study only the combinations as seen in table 2.6 were analysed. Thus prescriptions containing PPIs in combination with the following active ingredients were analysed: amoxicillin, bismuth, clarithromycin, metronidazole, and tetracycline (refer to section 2.5.2.6). The combinations were classified as two-drug -, three-drug – and bismuth-based four-drug regimens.

Since no clinical data (diagnoses) were available on the database (refer to section 6.3) it was assumed for the purpose of this study that if a PPI was prescribed together with amoxicillin, bismuth, clarithromycin, metronidazole, and tetracycline, it was for the treatment of *H.pylori*. Therefore the relevance of some of the prescribing patterns could not be determined.

Sometimes it happened that a combination was classified as a two-drug regimen but the combination contained three active ingredients (refer to Appendix F) or a combination was classified as a three-drug regimen but the combination contained four active ingredients (refer to Appendix F). Whilst this effect could not be further investigated with available information, this might be due to the occurrence of the same active ingredient twice on one prescription or that two different proton pump inhibitors (PPIs) were prescribed. Possible explanations for the double appearance of the same active ingredient on a prescription included: two different strengths of the same product were prescribed, the pharmacy that dispensed the prescription did not have the correct size packaging in stock or two different trade names containing the same active ingredient were prescribed.

5.7.1 PREVALENCE AND USAGE PATTERNS FOR PPI-BASE TWO-DRUG REGIMEN

Table 5.35 provides combination therapy for the eradication of *H.pylori*, classified as two-drug regimen (refer to table 2.6), for the five study years.

Table 5.35: Combination therapy for the eradication of *H.pylori*, classified as two-drug regimen, for the five study years.

Year	Active ingredient	Active ingredient	Number of prescriptions	Prevalence %	Average cost (R) per combination	Std dev $\pm$	Total cost (R)	Cost %	CPI
Clarithromycin/PPI									
2001	Clarithromycin	Lansoprazole	362	36.38	706.82	218.31	255 869.26	38.24	1.05
		Omeprazole	377	37.89	648.67	218.98	244 550.05	36.55	0.96
		Pantoprazole	168	16.88	687.66	176.65	115 527.28	17.27	1.02
		Rabeprazole	88	8.84	603.60	239.34	53 116.83	7.94	0.90
2002	Clarithromycin	Esomeprazole	209	17.97	763.94	216.35	159 663.40	19.04	1.06
		Lansoprazole	303	26.05	790.99	278.27	239 669.05	28.58	1.10
		Omeprazole	359	30.87	642.50	287.41	230 657.85	27.51	0.89
		Pantoprazole	170	14.62	726.45	267.94	123 495.74	14.73	1.01
		Rabeprazole	122	10.49	697.49	279.13	85 094.03	10.15	0.97
2004	Clarithromycin	Esomeprazole	440	23.27	647.31	268.12	284 815.72	21.15	0.91
		Lansoprazole	440	23.27	766.97	273.29	337 466.67	25.07	1.08
		Omeprazole	502	26.55	709.50	342.85	356 170.08	26.45	1.00
		Pantoprazole	299	15.81	658.67	262.13	196 942.62	14.63	0.93
		Rabeprazole	210	11.11	813.97	327.13	170 933.29	12.70	1.14
2005	Clarithromycin	Esomeprazole	289	19.13	582.86	254.79	168 446.04	18.32	0.96
		Lansoprazole	217	14.36	764.43	314.12	165 880.24	18.04	1.26
		Omeprazole	544	36.00	482.05	242.20	262 233.82	28.52	0.79
		Pantoprazole	291	19.26	662.08	278.37	192 665.25	20.95	1.09
		Rabeprazole	170	11.25	766.42	422.57	130 291.08	14.17	1.26
2006	Clarithromycin	Esomeprazole	241	18.01	590.87	156.66	142 400.47	25.39	1.41
		Lansoprazole	108	8.07	284.75	187.28	30 753.05	5.48	0.68
		Omeprazole	740	55.31	342.24	172.13	253 258.19	45.16	0.82
		Pantoprazole	150	11.21	501.06	140.48	75 158.53	13.40	1.20
		Rabeprazole	99	7.40	597.94	157.84	59 195.73	10.56	1.43

Table 5.35 (Continued): Combination therapy for the eradication of *H.pylori*, classified as two-drug regimen, for the five study years.

Year	Active ingredient	Active ingredient	Number of prescriptions	Prevalence %	Average cost per combination	Std dev $\pm$	Total cost	Cost %	CPI
Amoxicillin/PPI									
2004	Amoxicillin	Omeprazole	1	100.00	75.90	0.00	75.90	100.00	1.00

% - The number of prescriptions claimed (prevalence) for the specific period (year) divided by the total number of prescriptions containing PPIs (refer to table 5.2) for the corresponding year multiplied by hundred.

Cost% - The cost of a specific combination claimed during the specific period (year) divided by the total cost of all PPI containing prescriptions claimed (refer to table 5.2) during the corresponding year multiplied by hundred.

CPI - The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.35 shows that the combination of a PPI with clarithromycin was the two-drug regimen most often prescribed. The most popular clarithromycin and PPI combination was the combination of clarithromycin and omeprazole during the five study years. Amoxicillin was only prescribed once, during 2004, in combination with omeprazole.

The average cost for the combinations of, clarithromycin with lansoprazole, and, clarithromycin with omeprazole, revealed a practical significant decrease ($d > 0.8$) from 2001 to 2006 and from 2004 to 2006. The average cost for the combination of clarithromycin with pantoprazole revealed a practical significant decrease from 2001 to 2006 ($d = 1.06$) (refer to section 4.7.3.4).

5.7.2 PREVALENCE AND USAGE PATTERNS FOR PPI-BASE THREE-DRUG REGIMEN

Table 5.36 provides combination therapy for the eradication of *H.pylori*, classified as three-drug regimen (refer to table 2.6), for the five study years.

Table 5.36: Combination therapy for the eradication of *H.pylori*, classified as three-drug regimen, for the five study years.

Year	Active ingredient	Active ingredient	Active ingredient	Number of prescriptions	Prevalence %	Average cost (R) per combination	Std dev ±	Total cost (R)	Cost %	CPI
Clarithromycin/Metronidazole/PPI										
2001	Clarithromycin	Metronidazole	Lansoprazole	38	31.15	800.44	271.25	30 416.84	33.18	1.07
			Omeprazole	43	35.26	688.62	302.05	29 610.59	32.30	0.92
			Pantoprazole	23	18.85	813.01	195.85	18 699.22	20.40	1.08
			Rabeprazole	18	14.75	719.51	212.76	12 951.11	14.13	0.96
2002	Clarithromycin	Metronidazole	Esomeprazole	41	21.81	1 054.00	337.01	43 214.01	27.03	1.24
			Lansoprazole	46	24.47	801.12	338.22	36 851.69	23.05	0.94
			Omeprazole	51	27.13	683.43	331.96	34 855.14	21.80	0.80
			Pantoprazole	24	12.77	871.50	236.56	20 915.90	13.08	1.02
			Rabeprazole	26	13.83	924.41	281.34	24 034.65	15.03	1.09
2004	Clarithromycin	Metronidazole	Esomeprazole	66	27.05	695.42	276.06	45 897.83	22.98	0.85
			Lansoprazole	46	18.85	841.01	247.42	38 686.53	19.37	1.03
			Omeprazole	43	17.62	925.13	492.52	39 780.46	19.91	1.13
			Pantoprazole	51	20.90	835.91	316.45	42 631.56	21.34	1.02
			Rabeprazole	38	15.57	862.52	292.48	32 775.84	16.41	1.05
2005	Clarithromycin	Metronidazole	Esomeprazole	45	20.09	546.54	195.23	24 594.41	16.17	0.80
			Lansoprazole	39	17.41	829.08	286.87	32 334.26	21.26	1.22
			Omeprazole	54	24.11	549.50	271.72	29 673.14	19.51	0.81
			Pantoprazole	43	19.20	689.45	253.41	29 646.23	19.49	1.02
			Rabeprazole	43	19.20	834.03	230.71	35 863.19	23.58	1.23
2006	Clarithromycin	Metronidazole	Esomeprazole	30	15.08	580.28	124.47	17 408.52	18.88	1.25
			Lansoprazole	31	15.58	328.65	220.63	10 188.11	11.05	0.71
			Omeprazole	84	42.21	377.85	168.23	31 739.27	34.43	0.82
			Pantoprazole	20	10.05	487.52	123.98	9 750.33	10.58	1.05
			Rabeprazole	34	17.09	679.46	193.14	23 101.57	25.06	1.47

% - The number of prescriptions claimed (prevalence) for the specific period (year) divided by the total number of prescriptions containing PPIs (refer to table 5.2) for the corresponding year multiplied by hundred.

Cost% - The cost of a specific combination claimed during the specific period (year) divided by the total cost of all PPI containing prescriptions claimed (refer to table 5.2) during the corresponding year multiplied by hundred.

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.36 shows that the combination of a PPI with clarithromycin and metronidazole was the only three-drug regimen prescribed during the study years. The most popular clarithromycin, metronidazole, PPI combination was the combination of clarithromycin, metronidazole and omeprazole. The combination of clarithromycin, metronidazole and omeprazole was the combination with the highest number of prescriptions during 2001, 2002, 2005 and 2006. Clarithromycin, metronidazole and esomeprazole was the combination with the highest number of prescriptions during 2004.

In a single blind, prospectively randomised, parallel group, comparative, multicentre study was done by Misiewicz *et al.* (1997:739). which compared four treatment regimens lasting seven days of a PPI and two antibiotics in the eradication of *H.pylori*. It was concluded that all four treatment regimens were safe and efficacious in the eradication of *H.pylori* in patients with duodenal ulcer or non-ulcer gastritis, or both. The four treatment regimens were: LAC, LAM, LCM and OAM, where L is 30mg lansoprazole twice daily, A is 1g of amoxicillin twice daily, M is 400mg of metronidazole twice daily, C is 250mg of clarithromycin twice daily and O is 20mg of omeprazole twice daily (refer to section 2.5.2.6).

The active ingredients, amoxicillin, clarithromycin and omeprazole, are combined in Losec Triple Pack®. This three-drug regimen has already been discussed in section 5.5.3.2.

The average cost for the combinations of ,clarithromycin, metronidazole with lansoprazole, and, clarithromycin, metronidazole with omeprazole, as well as clarithromycin, metronidazole with pantoprazole revealed a practical significant decrease ($d > 0.8$) from 2001 to 2006 and from 2004 to 2006 (refer to section 4.7.3.4).

5.7.3 PREVALENCE AND USAGE PATTERNS FOR BISMUTH-BASED FOUR-DRUG REGIMEN

Table 5.37 provides combination therapy for the eradication of *H.pylori*, classified as bismuth-based four-drug regimen (refer to table 2.6), for the five study years.

Table 5.37: Combination therapy for the eradication of *H.pylori*, classified as bismuth-based four-drug regimen, for the five study years.

Year	Active ingredients	Active ingredient	Number of prescriptions	Prevalence %	Average cost (R) per combination	Std dev ±	Total cost (R)	Cost %	CPI
Bismuth/Clarithromycin/Metronidazole/PPI									
2001	Bismuth/Clarithromycin/Metronidazole	Omeprazole	1	50.00	846.65	0.00	848.65	41.35	0.83
		Rabeprazole	1	50.00	1 203.60	0.00	1 203.60	58.65	1.17
2002	Bismuth/Clarithromycin/Metronidazole	Omeprazole	1	50.00	785.32	0.00	785.32	37.23	0.74
		Pantoprazole	1	50.00	1 323.88	0.00	1 323.88	62.77	1.26
2004	Bismuth/Clarithromycin/Metronidazole	Esomeprazole	2	50.00	774.57	28.63	1 549.13	66.41	1.33
		Lansoprazole	2	50.00	391.75	246.36	783.53	33.59	0.67
2005	Bismuth/Clarithromycin/Metronidazole	Lansoprazole	4	80.00	545.93	47.45	2 183.72	94.48	1.18
		Pantoprazole	1	20.00	127.65	0.00	127.65	5.52	0.28
2006	Bismuth/Clarithromycin/Metronidazole	Esomeprazole	1	50.00	622.37	0.00	622.37	48.00	0.96
		Lansoprazole	1	50.00	674.23	0.00	674.23	52.00	1.04
Bismuth/Clarithromycin/Tetracycline/PPI									
2002	Bismuth/Clarithromycin/Tetracycline	Omeprazole	1	100.00	476.90	0.00	476.90	100.00	1.00

Bismuth/Clarithromycin/Metronidazole is three separate medicine items.

Bismuth/Clarithromycin/Tetracycline is three separate medicine items.

% - The number of prescriptions claimed (prevalence) for the specific period (year) divided by the total number of prescriptions containing PPIs (refer to table 5.2) for the corresponding year multiplied by hundred.

Cost% - The cost of a specific combination claimed during the specific period (year) divided by the total cost of all PPI containing prescriptions claimed (refer to table 5.2) during the corresponding year multiplied by hundred.

CPI - The cost % divided by the prevalence % (refer to section 4.6.4).

Table 5.37 shows that only 16 prescriptions contained bismuth-based four-drug regimens during the study years. Thus the bismuth combination was not popular for the eradication of *H.pylori*. However, the bismuth-based four-drug regimen most often prescribed was the combination of a PPI with bismuth, clarithromycin and metronidazole. The prevalence of prescriptions, containing bismuth-based four-drug regimens for the eradication of *H.pylori*, was the highest during 2005 and was the combination of bismuth, clarithromycin, metronidazole with lansoprazole. The combination of a PPI with bismuth, clarithromycin and tetracycline was only prescribed once during 2002.

The average cost for the combination of bismuth, clarithromycin, metronidazole with lansoprazole revealed a practical significant increase ($d > 0.8$) from 2004 to 2006 ($d = 1.15$) (refer to section 4.7.3.4).

Summary

Table 5.38 provides a summary of the prevalence percentage of the different two-drug -, three-drug and bismuth-based four-drug regimens used in the eradication of *H.pylori*, for the five study years.

Table 5.38: A summary of the prevalence percentage of the different two-drug -, three-drug and bismuth-based four-drug regimens used in the eradication of *H.pylori*, for the five study years.

Year	Number of prescriptions containing PPIs	Number of prescriptions: <i>H.pylori</i> eradication therapy	Two-drug regimen		Three-drug regimen	Bismuth-based four drug regimen	
			Number of prescriptions Clarithromycin/PPI	Number of prescriptions Amoxicillin/PPI	Number of prescriptions Clarithromycin/ Metronidazole/PPI	Number of prescriptions Bismuth/Clarithromycin/ Metronidazole/PPI	Number of prescriptions Bismuth/Clarithromycin/ Tetracycline/PPI
2001	N = 39 621	2.72% (n = 1 079)	2.41% (n = 955)	(n = 0)	0.31% (n = 122)	0.01% (n = 2)	(n = 0)
2002	N = 54 221	2.50% (n = 1 354)	2.14% (n = 1 163)	(n = 0)	0.35% (n = 188)	0.00% (n = 2)	0.00% (n = 1)
2004	N = 71 049	3.01% (n = 2 140)	2.66% (n = 1 891)	0.00% (n = 1)	0.34% (n = 244)	0.01% (n = 4)	(n = 0)
2005	N = 48 515	3.69% (n = 1 740)	3.11% (n = 1 511)	(n = 0)	0.46% (n = 224)	0.01% (n = 5)	(n = 0)
2006	N = 30 442	5.05% (n = 1 539)	4.40% (n = 1 338)	(n = 0)	0.65% (n = 199)	0.01% (n = 2)	(n = 0)

% - The number of prescriptions containing *H.pylori* eradication therapy claimed for the specific period (year) divided by the total number of prescriptions containing PPIs for the corresponding year multiplied by hundred

Table 5.38 shows that the prevalence of the two-drug regimens was the highest during the five study years. Although the literature study had shown that PPI-based three-drug regimen was most efficient, better tolerated, simpler and had better adherence (refer to section 2.5.2.6). The MACH 1 study has compared different combinations of omeprazole and two antimicrobials as PPI triple therapy (first-line treatment for *H.pylori* infection) (Sung *et al.*, 1999:1083).

The prevalence of prescriptions, containing the combination of a PPI with clarithromycin, increased with 1.99% from 2001 to 2006. While the prevalence of prescriptions, containing the combination of a PPI with clarithromycin and metronidazole, increased with 0.34% from 2001 to 2006. The prevalence of prescriptions, containing the combination of a PPI with bismuth, clarithromycin and metronidazole stayed reasonably constant during the five study years.

According to a study conducted by Farmer (2001:157) the treatment regimens for *H.pylori* contributed to 0.86% (where a PPI was simultaneously used with amoxicillin and clarithromycin), to 0.08% (where a PPI was used simultaneously with amoxicillin and metronidazole) and to 0.00% (where a PPI was used simultaneously with bismuth, tetracycline and metronidazole) of all PPI containing prescriptions.

The *H.pylori* eradication treatments, which included different antibiotics, increased from 2.72% in 2001 to 5.05% in 2006 (table 5.38). According to a study conducted by Farmer (2001:208) who used a medicine claims database, Interpharm Data systems® in South Africa, prescriptions, containing *H.pylori* eradication therapy, contributed to 0.90% of the total PPI prescriptions.

5.8 UTILISATION AND COST OF ACID REDUCING MEDICINE

5.8.1 UTILISATION AND COST OF ACID REDUCING MEDICINE ITEMS IN TERMS OF PRESCRIBED DAILY DOSE (PDD)

In the following section the consumption and utilisation of histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) were calculated in terms of the prescribed daily dose (PDD). The PDD was determined between the innovator and generic items for each active ingredient and strength. The effect sizes (d-value) were also calculated between the average cost of innovator and generic medicine items for each active ingredient and strength.

The PDD is the average daily amount of the medicine item that is actually prescribed for a given period of time (refer section 3.3.5).

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or PDD. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations (WHO, 2007a) (refer to section 3.3.5).

In this study the average number of tablets/capsules per prescription (per month) of each active ingredient was used to calculate the average number of tablets/capsules and the average strength per day (in mg) that a patient received. For the purpose of this analysis the active ingredients were divided into innovator and generic medicine items. The average number of tablets/capsules per day was determined by dividing the average number of tablets/capsules (per month) by the median (refer to section 4.7.3.5). The median represents the number of days up to 50% of the study population (refer to section 4.4) received the relevant medicine item (active ingredient and strength). By multiplying the average number of tablets/capsules per day with the strength of the active ingredient, the average strength per day that a patient received was determined.

Table 5.39 provides the PDD for H₂RAs and PPIs, according to innovator and generic medicine items, during 2001.

Table 5.39: PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2001.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription							
				Average number	Std dev ±	Median	PDD mg/day	Average cost (R)	Std dev ±	Total Cost	d-value
Cimetidine 200mg	Tab	Innovator	29	73.90	69.16	60.00	246.32	352.19	367.44	10 213.64	
Cimetidine 200mg	Tab	Generic	1 193	39.81	23.14	30.00	265.43	76.39	46.86	91 133.89	0.75
Cimetidine 400mg	Tab	Innovator	39	35.33	20.13	30.00	471.11	274.52	128.94	10 706.15	
Cimetidine 400mg	Tab	Generic	3 382	38.20	19.14	30.00	509.32	182.20	85.85	619 571.36	0.71
Nizatidine 150mg	Cap	Innovator	45	29.96	25.85	14.00	320.95	243.82	209.52	10 971.91	-
Ranitidine 75mg	Tab	Innovator	908	19.33	13.06	15.00	96.65	83.76	43.02	76 055.94	-
Ranitidine 75mg	Tab	Generic	119	18.66	15.95	12.00	116.60	68.87	52.89	8 195.54	0.28
Ranitidine 150mg	Tab	Innovator	523	35.98	17.66	30.00	179.88	240.08	112.59	125 561.22	
Ranitidine 150mg	Tab	Generic	3 160	36.21	18.50	30.00	181.03	169.77	95.03	536 488.63	0.62
Ranitidine 300mg	Tab	Innovator	187	25.80	8.44	30.00	258.02	312.78	119.47	58 489.70	
Ranitidine 300mg	Tab	Generic	1 179	25.47	10.24	30.00	254.70	220.81	93.34	260 339.26	0.76
Ranitidine eff 150mg	Tab	Innovator	1 501	21.73	12.65	20.00	162.95	159.01	84.20	238 666.59	-
Ranitidine eff 300mg	Tab	Innovator	206	25.44	8.71	30.00	254.42	427.16	135.16	8 7994.10	-
Famotidine 20mg	Tab	Innovator	40	22.10	8.76	28.00	15.79	255.90	101.74	10 235.59	-
Famotidine 40mg	Tab	Innovator	44	24.02	7.10	28.00	34.32	601.91	191.01	2 6484.20	-
Omeprazole 10mg	Tab	Innovator	3 354	25.51	7.16	28.00	9.11	286.17	77.92	959 827.11	
Omeprazole 10mg	Cap	Generic	153	23.61	9.51	30.00	7.87	210.72	82.76	32 240.29	0.91
Omeprazole 20mg	Tab	Innovator	8 361	22.04	8.48	28.00	15.75	413.35	152.36	3 456 060.37	
Omeprazole 20mg	Cap	Generic	518	21.34	9.69	21.00	20.32	305.14	161.27	158 061.25	0.67
Omeprazole 40mg	Tab	Innovator	303	16.69	7.86	14.00	47.69	630.56	283.43	191 060.01	-
Omeprazole 20mg amoxicillin/clarithromycin	Cap	Innovator	266	46.40	9.75	49.00	18.94	678.84	121.38	180 572.15	-
Pantoprazole 20mg	Tab	Innovator	468	23.78	8.25	28.00	16.98	249.39	83.15	116 713.16	-
Pantoprazole 40mg	Tab	Innovator	5 517	21.81	8.33	28.00	31.16	383.90	135.99	2 117 996.54	-
Rabeprazole 10mg	Tab	Innovator	2 231	25.15	7.16	28.00	8.98	233.52	64.28	520 987.63	-

Table 5.39 (Continued): PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2001.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total Cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Rabeprazole 20mg	Tab	Innovator	3 703	21.05	8.76	28.00	15.04	318.70	133.45	1 180 139.47	-
Lansoprazole 15mg	Cap	Innovator	5 151	26.29	6.27	28.00	14.09	287.33	78.86	1 480 051.48	-
Lansoprazole 30mg	Cap	Innovator	9 704	21.97	8.55	28.00	23.54	398.42	151.63	3 866 295.47	-

DF – Dosage form

PDD (mg/day) – The average number of tablets/capsules per prescription for a specific active ingredient divided by the corresponding median multiply by the strength of the relative active ingredient

The effect sizes (d-values) were calculated between the average cost of innovator and generic medicine item for each active ingredient and strength (refer to section 4.7.3.4).

Table 5.39 shows that the PDD of the following generic medicine items was greater than the PDD of the innovator medicine items: cimetidine 200mg, cimetidine 400mg, ranitidine 75mg, ranitidine 150mg and omeprazole 20mg. Thus the average daily amount of these generic medicine items prescribed was greater than the average daily amount of the innovator medicine items.

The difference between the average cost of innovator and generic medicine items was of no practical significance during 2001 (table 5.39).

Table 5.40 provides the PDD for H₂RAs and PPIs, according to innovator and generic medicine items, during 2002.

Table 5.40: PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2002.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription							
				Average number	Std dev ±	Median	PDD mg/day	Average cost (R)	Std dev ±	Total cost	d-value
Cimetidine 200mg	Tab	Innovator	9	29.44	19.11	30.00	196.30	90.52	63.18	84.67	
Cimetidine 200mg	Tab	Generic	1 478	38.17	22.65	30.00	254.50	65.13	36.83	96 266.91	0.40
Cimetidine 400mg	Tab	Innovator	27	31.52	15.53	30.00	420.25	246.24	117.92	7 134.45	
Cimetidine 400mg	Tab	Generic	3 803	38.07	20.29	30.00	507.59	180.33	91.21	685 801.26	0.56
Nizatidine 150mg	Cap	Innovator	183	24.48	13.60	28.00	131.12	248.18	149.56	45 416.38	-
Ranitidine 75mg	Tab	Innovator	1 006	18.75	12.43	14.00	100.45	80.17	44.43	80 646.53	
Ranitidine 75mg	Tab	Generic	427	20.75	14.36	12.00	129.71	63.19	41.77	26 981.41	0.38
Ranitidine 150mg	Tab	Innovator	538	34.79	17.91	30.00	173.95	249.45	131.85	134 206.54	
Ranitidine 150mg	Tab	Generic	4 523	35.30	18.68	30.00	176.51	160.48	89.36	725 867.79	0.67
Ranitidine 300mg	Tab	Innovator	260	27.77	10.95	30.00	277.65	365.78	199.59	95 103.76	
Ranitidine 300mg	Tab	Generic	1 530	26.32	10.59	30.00	263.15	175.76	70.33	268 906.24	0.95
Ranitidine eff 150mg	Tab	Innovator	1 838	23.48	12.89	15.00	234.78	199.26	110.60	366 239.26	-
Ranitidine eff 300mg	Tab	Innovator	378	25.39	9.15	30.00	253.94	428.95	151.01	162 142.35	-
Ranitidine bismuth citrate 400mg	Tab	Innovator	33	23.33	6.70	28.00	333.33	288.23	82.04	9 511.46	-
Famotidine 20mg	Tab	Innovator	4	10.25	4.35	10.50	19.52	117.79	49.98	471.15	-
Famotidine 40mg	Tab	Innovator	67	22.06	9.07	28.00	31.51	460.60	369.20	30 859.96	-
Esomeprazole 20mg	Tab	Innovator	1 924	22.94	8.54	28.00	16.38	279.97	98.81	538 666.27	-
Esomeprazole 40mg	Tab	Innovator	4 060	18.81	8.73	14.00	53.74	368.23	160.21	1 494 997.59	-
Omeprazole 10mg	Tab	Innovator	3 336	26.24	7.81	28.00	9.37	302.90	89.25	1 010 473.75	
Omeprazole 10mg	Cap	Generic	1 380	26.73	9.47	30.00	8.91	218.01	74.59	300 858.80	0.95
Omeprazole 20mg	Tab	Innovator	7 452	22.76	9.05	28.00	16.26	437.64	170.57	3 261 315.59	
Omeprazole 20mg	Cap	Generic	3 971	22.54	9.51	30.00	15.03	308.67	125.90	1 225 733.21	0.76

Table 5.40 (Continued): PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2002.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Omeprazole 40mg	Tab	Innovator	186	19.19	10.60	14.00	54.82	738.17	409.75	137 299.35	-
Omeprazole 20mg /amoxicillin/clarithromycin	Cap	Innovator	278	47.50	7.14	49.00	19.39	740.31	99.74	205 806.22	-
Pantoprazole 20mg	Tab	Innovator	2 014	25.72	7.44	28.00	18.37	252.52	70.18	508 576.22	-
Pantoprazole 40mg	Tab	Innovator	5 537	22.09	8.24	28.00	31.56	406.06	140.57	2 248 344.08	-
Rabeprazole 10mg	Tab	Innovator	2 864	25.95	6.94	28.00	9.27	288.25	72.54	825 553.31	-
Rabeprazole 20mg	Tab	Innovator	4 401	20.75	8.95	28.00	14.82	381.87	161.92	1 680 621.53	-
Lansoprazole 15mg	Cap	Innovator	6 322	26.97	6.08	28.00	14.45	327.87	74.55	2 072 788.25	-
Lansoprazole 30mg	Cap	Innovator	10 643	22.44	8.52	28.00	24.04	445.06	161.52	4 736 747.05	-

DF – Dosage form

PDD (mg/day) – The average number of tablets/capsules per prescription for a specific active ingredient divided by the corresponding median multiply by the strength of the relative active ingredient

The effect sizes (d-values) were calculated between the average cost of innovator and generic medicine item for each active ingredient and strenght (refer to section 4.7.3.4).

Table 5.40 shows that the PDD of the following generic medicine items was greater than the PDD of the innovator medicine items: cimetidine 200mg, cimetidine 400mg, ranitidine 75mg and ranitidine 150mg. Thus the average daily amount of these generic medicine items prescribed was greater than the average daily amount of the innovator medicine items.

There was a practical significant difference between the average cost of the innovator and generic medicine items containing ranitidine 300mg ($d = 0.95$), omeprazole 10mg ($d = 0.95$) and omeprazole 20mg ($d = 0.76$) (table 5.40) (refer to section 4.7.3.4).

Table 5.41 provides the PDD for H₂RAs and PPIs, according to innovator and generic medicine items, during 2004.

Table 5.41: PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2004.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Cimetidine 200mg	Tab	Innovator	11	28.82	17.93	30.00	192.12	115.54	95.27	1 270.95	
Cimetidine 200mg	Tab	Generic	1 440	36.01	23.17	30.00	240.04	34.42	26.55	49 601.55	0.85
Cimetidine 400mg	Tab	Innovator	24	33.88	21.98	30.00	451.67	221.55	231.98	5 317.15	
Cimetidine 400mg	Tab	Generic	3 809	38.58	20.54	30.00	514.40	80.37	83.27	306 118.29	0.61
Nizatidine 150mg	Cap	Innovator	233	24.21	14.16	14.00	259.44	221.78	134.62	51 674.85	-
Ranitidine 75mg	Tab	Innovator	327	14.41	9.47	10.00	108.07	62.85	38.82	20 551.34	
Ranitidine 75mg	Tab	Generic	427	19.20	11.32	12.00	119.98	40.01	30.29	17 085.83	0.59
Ranitidine 150mg	Tab	Innovator	445	40.38	20.56	30.00	201.89	319.39	196.03	142 127.15	
Ranitidine 150mg	Tab	Generic	7 200	37.19	19.15	30.00	185.95	77.09	62.98	555 031.04	1.24
Ranitidine 300mg	Tab	Innovator	282	30.88	13.47	30.00	308.79	506.11	221.98	142 722.54	
Ranitidine 300mg	Tab	Generic	2 896	27.21	10.34	30.00	272.09	106.26	77.94	307 743.04	1.80
Ranitidine eff 75mg	Tab	Innovator	163	16.74	14.11	12.00	104.60	62.78	50.40	10 233.36	-
Ranitidine eff 150mg	Tab	Innovator	2 662	24.06	13.94	15.00	240.60	260.12	156.84	692 443.26	-
Ranitidine eff 300mg	Tab	Innovator	652	23.93	9.85	30.00	239.28	497.65	217.61	324 468.17	-
Famotidine 40mg	Tab	Innovator	107	21.71	3.84	21.00	41.36	484.60	100.72	51 851.67	-
Esomeprazole 20mg	Tab	Innovator	8 972	24.97	8.85	28.00	17.84	240.23	89.23	2 155 314.25	-
Esomeprazole 40mg	Tab	Innovator	10 360	21.62	9.51	28.00	30.88	331.16	156.55	3 430 848.83	-
Omeprazole 10mg	Tab	Innovator	2746	25.71	8.59	28.00	9.18	267.43	102.54	734 372.36	
Omeprazole 10mg	Cap	Generic	112	25.59	16.07	30.00	8.53	121.12	66.44	13 565.08	1.43
Omeprazole 20mg	Tab	Innovator	6437	24.56	10.38	28.00	17.54	419.07	193.92	2 697 546.33	
Omeprazole 20mg	Cap	Generic	3400	24.83	10.38	28.00	17.73	113.44	74.67	385 693.91	1.58
Omeprazole 40mg	Tab	Innovator	588	21.60	8.06	28.00	30.86	743.16	360.47	436 977.47	
Omeprazole 20mg /amoxicillin/clarithromycin	Cap	Innovator	46	47.63	6.54	49.00	19.44	676.80	194.10	31 132.77	-

Table 5.41 (Continued): PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2004.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Pantoprazole 20mg	Tab	Innovator	5 735	25.94	7.63	28.00	18.53	202.34	71.19	1 160 425.61	
Pantoprazole 40mg	Tab	Innovator	8 528	23.49	8.95	28.00	33.56	336.40	142.53	2 868 817.65	
Rabeprazole 10mg	Tab	Innovator	2 113	25.50	7.58	28.00	9.11	227.18	71.07	480 035.50	
Rabeprazole 20mg	Tab	Innovator	4 848	22.60	9.17	28.00	16.14	376.51	159.37	1 825 301.88	
Lansoprazole 15mg	Cap	Innovator	6 809	26.85	8.20	28.00	14.38	278.79	95.91	1 898 256.77	
Lansoprazole 30mg	Cap	Innovator	10 574	23.30	9.52	28.00	24.96	386.94	164.00	4 091 488.46	

DF – Dosage form

PDD (mg/day) – The average number of tablets/capsules per prescription for a specific active ingredient divided by the corresponding median multiply by the strength of the relative active ingredient

The effect sizes (d-values) were calculated between the average cost of innovator and generic medicine item for each active ingredient and strength (refer to section 4.7.3.4).

Table 5.41 shows that the PDD of the following generic medicine items was greater than the PDD of the innovator medicine items: cimetidine 200mg, cimetidine 400mg and ranitidine 75mg. Thus the average daily amount of these generic medicine items prescribed was greater than the average daily amount of the innovator medicine items.

There was a practical significant difference between the average cost of the innovator and generic medicine items containing cimetidine 200mg ($d = 0.85$), ranitidine 150mg ($d = 1.24$), ranitidine 300mg ($d = 1.80$), omeprazole 10mg ($d = 1.43$) and omeprazole 20mg ($d = 1.58$) (table 5.41) (refer to section 4.7.3.4).

Table 5.42 provides the PDD for H₂RAs and PPIs, according to innovator and generic medicine items, during 2005.

Table 5.42: PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2005.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Cimetidine 200mg	Tab	Innovator	3	23.33	5.77	20.00	233.33	79.51	55.99	238.53	
Cimetidine 200mg	Tab	Generic	570	36.72	27.15	30.00	244.83	19.60	14.02	11 171.19	1.07
Cimetidine 400mg	Tab	Innovator	20	50.30	22.41	60.00	335.33	118.49	213.46	2 369.70	
Cimetidine 400mg	Tab	Generic	1 911	41.96	23.18	30.00	559.50	29.53	16.97	56 438.29	0.42
Nizatidine 150mg	Cap	Innovator	174	22.30	12.41	14.00	238.92	174.67	94.60	30 392.10	-
Ranitidine 75mg	Tab	Innovator	237	16.30	12.15	10.00	122.22	63.41	42.46	15 028.37	
Ranitidine 75mg	Tab	Generic	151	19.79	12.53	12.00	123.72	29.16	20.86	4 403.86	0.81
Ranitidine 150mg	Tab	Innovator	236	37.66	19.78	30.00	188.31	302.00	193.56	71 272.64	
Ranitidine 150mg	Tab	Generic	4 586	39.14	19.53	30.00	195.71	50.72	32.96	232 587.11	1.30
Ranitidine 300mg	Tab	Innovator	210	37.55	20.83	30.00	375.52	601.72	235.66	126 361.61	
Ranitidine 300mg	Tab	Generic	2 526	30.89	13.06	30.00	308.88	46.68	19.74	117 924.19	2.36
Ranitidine eff 75mg	Tab	Innovator	70	19.73	10.62	24.00	61.65	69.99	35.61	4 899.48	-
Ranitidine eff 150mg	Tab	Innovator	3 448	24.70	14.29	15.00	246.97	280.53	163.22	96 280.67	-
Ranitidine eff 300mg	Tab	Innovator	954	23.21	9.37	30.00	232.15	506.76	193.46	483 451.69	-
Esomeprazole 20mg	Tab	Innovator	4 560	26.92	9.79	28.00	19.23	234.24	79.62	1 068 135.80	-
Esomeprazole 40mg	Tab	Innovator	5 970	24.53	11.51	28.00	35.05	330.33	150.26	1 972 059.51	-
Omeprazole 10mg	Tab	Innovator	870	25.30	10.29	28.00	9.04	210.53	84.81	183 159.89	
Omeprazole 10mg	Cap	Generic	524	27.62	10.65	30.00	9.21	124.96	47.83	65 476.92	1.09
Omeprazole 20mg	Tab	Innovator	1 349	28.27	13.18	28.00	20.19	324.97	188.09	438 381.14	
Omeprazole 20mg	Cap	Generic	12 586	27.10	9.07	28.00	19.36	117.32	67.76	1 476 605.36	1.10
Omeprazole 40mg	Tab	Innovator	289	24.21	7.58	28.00	34.58	843.63	292.91	43 808.18	-
Omeprazole 20mg /amoxicillin/clarithromycin	Cap	Innovator	2	49.00	0.00	49.00	20.00	609.90	0.00	1 219.80	-
Pantoprazole 20mg	Tab	Innovator	2 877	26.87	8.64	28.00	19.19	185.51	59.03	533 703.20	-

Table 5.42 (Continued): PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2005.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Pantoprazole 40mg	Tab	Innovator	5 369	25.45	8.04	28.00	36.36	328.75	111.97	1 765 082.12	-
Rabeprazole 10mg	Tab	Innovator	1 006	26.33	7.58	28.00	9.40	246.65	75.46	248 130.57	-
Rabeprazole 20mg	Tab	Innovator	4 073	24.93	10.54	28.00	17.81	422.63	172.19	1 721 376.37	-
Lansoprazole 15mg	Cap	Innovator	2 474	27.49	10.59	28.00	14.73	260.83	102.23	645 301.74	
Lansoprazole 15mg	Cap	Generic	347	26.17	8.67	30.00	13.08	115.75	56.95	40 165.00	1.42
Lansoprazole 30mg	Cap	Innovator	5 490	26.29	9.48	28.00	28.16	414.96	151.52	2 278 151.84	
Lansoprazole 30mg	Cap	Generic	852	25.43	8.35	30.00	25.43	134.80	84.78	114 852.85	1.85

DF – Dosage form

PDD (mg/day) – The average number of tablets/capsules per prescription for a specific active ingredient divided by the corresponding median multiply by the strength of the relative active ingredient

The effect sizes (d-values) were calculated between the average cost of innovator and generic medicine item for each active ingredient and strength (refer to section 4.7.3.4).

Table 5.42 shows that the PDD of the following generic medicine items was greater than the PDD of the innovator medicine items: cimetidine 200mg, cimetidine 400mg, ranitidine 150mg and omeprazole 10mg. Thus the average daily amount of these generic medicine items prescribed was greater than the average daily amount of the innovator medicine items.

There was a practical significant difference between the average cost of the innovator and generic medicine items containing cimetidine 200mg ($d = 1.07$), ranitidine 150mg ($d = 1.30$), ranitidine 300mg ($d = 2.36$), omeprazole 10mg ($d = 1.09$), omeprazole 20mg ($d = 1.10$), lansoprazole 15mg ($d = 1.42$) and lansoprazole 30mg ($d = 1.85$) (table 5.42) (refer to section 4.7.3.4).

Table 5.43 provides the PDD for H₂RAs and PPIs, according to innovator and generic medicine items, during 2006.

Table 5.43: PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2006.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription							
				Average number	Std dev ±	Median	PDD mg/day	Average cost (R)	Std dev ±	Total cost	d-value
Cimetidine 200mg	Tab	Generic	182	42.25	23.85	30.00	281.65	21.67	15.63	3 943.15	-
Cimetidine 400mg	Tab	Innovator	3	33.33	25.17	30.00	444.44	340.64	276.44	1 021.92	
Cimetidine 400mg	Tab	Generic	868	37.86	24.52	30.00	504.79	31.54	17.69	27 380.26	1.18
Nizatidine 150mg	Cap	Innovator	95	15.18	5.27	14.00	162.63	120.87	41.63	11 482.47	-
Ranitidine 75mg	Tab	Innovator	136	16.96	9.07	12.50	101.74	74.00	39.49	10 064.36	
Ranitidine 75mg	Tab	Generic	71	18.70	14.49	12.00	116.90	26.14	17.29	1 856.23	1.21
Ranitidine 150mg	Tab	Innovator	81	50.69	34.62	60.00	126.73	402.28	251.99	32 584.76	
Ranitidine 150mg	Tab	Generic	3 321	40.91	20.61	30.00	204.56	60.28	41.33	200 174.35	1.36
Ranitidine 300mg	Tab	Innovator	42	39.17	27.12	30.00	391.67	548.29	381.47	23 028.05	
Ranitidine 300mg	Tab	Generic	1 848	32.24	14.72	30.00	322.45	49.98	20.9	92 364.96	1.31
Ranitidine eff 75mg	Tab	Innovator	94	25.87	18.07	24.00	80.85	99.85	60.94	9 386.17	-
Ranitidine eff 150mg	Tab	Innovator	3 158	25.06	14.90	15.00	250.61	284.55	169.79	898 595.29	-
Ranitidine eff 300mg	Tab	Innovator	804	21.51	8.97	15.00	430.25	472.36	199.39	379 779.07	-
Esomeprazole 20mg	Tab	Innovator	1 375	30.04	11.56	28.00	21.45	288.14	90.59	96 192.31	-
Esomeprazole 40mg	Tab	Innovator	2 886	27.44	8.83	28.00	39.20	429.50	126.91	1 239 530.07	-
Omeprazole 10mg	Tab	Innovator	212	28.27	21.06	28.00	10.10	194.43	166.41	41 220.13	
Omeprazole 10mg	Cap	Generic	380	27.45	9.98	28.00	9.80	135.98	45.75	51 673.56	0.35
Omeprazole 20mg	Tab	Innovator	491	29.84	13.01	28.00	21.31	378.98	197.13	186 080.68	
Omeprazole 20mg	Cap	Generic	12 551	29.11	9.16	28.00	20.79	149.74	45.86	1 879 427.71	1.16
Omeprazole 40mg	Tab	Innovator	151	24.40	7.87	28.00	34.85	845.01	284.88	127 596.25	
Omeprazole 40mg	Tab	Generic	2	21.00	9.90	21.00	40.00	209.31	98.66	418.61	2.23
Pantoprazole 20mg	Tab	Innovator	705	28.37	8.31	28.00	20.27	199.88	59.48	140 912.64	
Pantoprazole 20mg	Tab	Generic	304	29.11	11.86	28.00	20.79	184.24	59.99	56 009.53	0.26

Table 5.43 (Continued): PDD for the active ingredients of H₂RAs and PPIs, according to innovator and generic medicine items, during 2006.

Active ingredient	DF	Innovator/ Generic	Prevalence	Quantity tablets/capsules per prescription				Average cost (R)	Std dev ±	Total cost	d-value
				Average number	Std dev ±	Median	PDD mg/day				
Pantoprazole 40mg	Tab	Innovator	1 762	27.54	9.11	28.00	39.34	364.13	106.82	641 602.34	
Pantoprazole 40mg	Tab	Generic	1 041	26.31	6.92	28.00	37.59	320.51	83.54	333 651.34	0.41
Rabeprazole 10mg	Tab	Innovator	416	28.51	9.74	28.00	10.18	292.91	85.78	121 850.73	-
Rabeprazole 20mg	Tab	Innovator	2 789	26.19	8.74	28.00	18.70	468.90	154.24	1 307 772.69	-
Lansoprazole 15mg	Cap	Innovator	277	33.14	15.79	28.00	17.75	278.53	127.63	77 151.60	
Lansoprazole 15mg	Cap	Generic	866	28.01	9.72	30.00	14.00	82.74	89.63	71 654.54	1.53
Lansoprazole 30mg	Cap	Innovator	744	30.85	13.80	28.00	33.05	393.64	206.99	292 870.45	
Lansoprazole 30mg	Cap	Generic	3 526	28.53	6.97	30.00	28.53	108.15	112.07	381 320.26	1.38

DF – Dosage form

PDD (mg/day) – The average number of tablets/capsules per prescription for a specific active ingredient divided by the corresponding median multiply by the strength of the relative active ingredient

The effect sizes (d-values) were calculated between the average cost of innovator and generic medicine item for each active ingredient and strength (refer to section 4.7.3.4).

Table 5.43 shows that the PDD of the following generic medicine items was greater than the PDD of the innovator medicine items: cimetidine 400mg, ranitidine 75mg, ranitidine 150mg, omeprazole 40mg, pantoprazole 20mg and rabeprazole 20mg. Thus the average daily amount of these generic medicine items prescribed was greater than the average daily amount of the innovator medicine items.

There was a practical significant difference between the average cost of the innovator and generic medicine items containing cimetidine 400mg ($d = 1.18$), ranitidine 75mg ($d = 1.21$), ranitidine 150mg ($d = 1.36$), ranitidine 300mg ($d = 1.31$), omeprazole 20mg ($d = 1.16$), omeprazole 40mg ($d = 2.23$), lansoprazole 15mg ($d = 1.53$) and lansoprazole 30mg ($d = 1.38$) (table 5.43) (refer to section 4.7.3.4).

Summary

Table 5.44 provides a summary of the PDD for the different active ingredients and their corresponding strengths according to innovator and generic medicine items during the five study years (compounded from table 5.39 to table 5.43).

Table 5.44: A summary of the PDD for the different active ingredients and their corresponding strengths (in mg) according to innovator and generic medicine items during the five study years: 2001, 2002, 2004, 2005 and 2006.

Active ingredient	DF	Innovator/ Generic	PDD				
			2001	2002	2004	2005	2006
Cimetidine 200mg	Tab	Innovator	246.00	196.30	192.12	233.33	0.00
Cimetidine 200mg	Tab	Generic	265.43	254.50	240.04	244.83	281.65
Cimetidine 400mg	Tab	Innovator	471.11	420.25	451.67	335.33	444.44
Cimetidine 400mg	Tab	Generic	509.32	507.59	514.40	559.50	504.79
Nizatidine 150mg	Cap	Innovator	320.95	131.12	259.44	238.92	162.63
Ranitidine 75mg	Tab	Innovator	96.65	100.45	108.07	122.22	101.74
Ranitidine 75mg	Tab	Generic	116.60	129.71	119.98	123.72	116.90
Ranitidine 150mg	Tab	Innovator	179.88	173.95	201.89	188.31	126.73
Ranitidine 150mg	Tab	Generic	181.03	176.51	185.95	195.71	204.56
Ranitidine 300mg	Tab	Innovator	258.02	277.65	308.79	375.52	391.67
Ranitidine 300mg	Tab	Generic	254.70	263.15	272.09	308.88	322.45
Ranitidine eff 75mg	Tab	Innovator	0.00	0.00	104.60	61.65	80.85
Ranitidine eff 150mg	Tab	Innovator	162.95	234.78	240.60	246.97	250.61
Ranitidine eff 300mg	Tab	Innovator	254.42	253.94	239.28	232.15	430.25
Ranitidine bismuth citrate 400mg	Tab	Innovator	0.00	333.33	0.00	0.00	0.00
Famotidine 20mg	Tab	Innovator	15.79	19.52	0.00	0.00	0.00
Famotidine 40mg	Tab	Innovator	34.32	31.50	41.36	0.00	0.00
Esomeprazole 20mg	Tab	Innovator	0.00	16.38	17.84	19.23	21.45
Esomeprazole 40mg	Tab	Innovator	0.00	53.74	37.88	35.05	39.20
Omeprazole 10mg	Tab	Innovator	9.11	9.37	9.18	9.04	10.10
Omeprazole 10mg	Cap	Generic	7.87	8.91	8.53	9.21	9.80
Omeprazole 20mg	Tab	Innovator	15.75	16.26	17.54	20.19	21.31
Omeprazole 20mg	Cap	Generic	20.32	15.03	17.73	19.36	20.79
Omeprazole 40mg	Tab	Innovator	47.69	54.82	30.86	34.58	34.85
Omeprazole 40mg	Tab	Generic	0.00	0.00	0.00	0.00	40.00
Pantoprazole 20mg	Tab	Innovator	16.98	18.37	18.53	19.19	20.27
Pantoprazole 20mg	Tab	Generic	0.00	0.00	0.00	0.00	20.79
Pantoprazole 40mg	Tab	Innovator	31.16	31.56	33.56	36.36	39.34
Pantoprazole 40mg	Tab	Generic	0.00	0.00	0.00	0.00	37.59
Rabeprazole 10mg	Tab	Innovator	8.98	9.27	9.11	9.40	10.18
Rabeprazole 20mg	Tab	Innovator	15.04	14.82	16.14	17.81	18.70
Lansoprazole 15mg	Cap	Innovator	14.09	14.45	14.38	14.73	17.75
Lansoprazole 15mg	Cap	Generic	0.00	0.00	0.00	13.08	14.00
Lansoprazole 30mg	Cap	Innovator	23.54	24.04	24.96	28.16	33.05
Lansoprazole 30mg	Cap	Generic	0.00	0.00	0.00	25.43	28.53

Table 5.44 shows that the PDD of the innovator medicine items containing nizatidine 150mg, decreased with 59.13% ($n = 189.83$) from 2001 to 2002 and then increased with 97.86% ($n = 128.32$) from 2002 to 2004. The PDD of the innovator medicine items containing nizatidine 150mg decreased with 49.33% ($n = 158.32$) from 2001 to 2006. The increase of the PDD from 2001 to 2002 might be explained by a combination of the decrease in the average number capsules (containing nizatidine 150mg) per month and an increase in the median. The average number of capsules (containing nizatidine 150mg) decreased with 18.29% from 2001 ($n = 29.96 \pm 25.85$) to 2002 ($n = 24.48 \pm 13.60$). While the median increased with 50.00% from 2001 ($n = 14$) to 2002 ($n = 28$) (refer to table 5.39 to table 5.43). The decrease in the PDD of the innovator medicine items, containing nizatidine 150mg, might be due to the decrease in the average number of capsules (containing nizatidine 150mg) from 2001 ($n = 29.96 \pm 25.85$) to 2006 ($n = 15.18 \pm 5.27$) (refer to table 5.39 to table 5.43).

The PDD of generic medicine items, containing ranitidine 75mg, increased with only 0.26% ($n = 0.30$) from 2001 to 2006 (table 5.44). This small increase might possibly be due to the fact that both the median and the average number of tablets of ranitidine 75mg (generic) stayed reasonably constant during the study years (refer to table 5.39 to table 5.43).

The PDD of innovator medicine items, containing ranitidine 300mg, increased with 51.80% ($n = 133.65$) from 2001 to 2006. The average number of tablets for the innovator medicine items, containing ranitidine 300mg, increased from 2001 ($n = 25.80 \pm 8.44$) to 2006 ($n = 39.17 \pm 39.17$) (refer to table 5.39 to table 5.43). This might be the reason for the increase in the PDD of these medicine items.

The PDD of ranitidine 150mg effervescent tablets (innovator) and ranitidine 300mg effervescent tablets (innovator) increased respectively with 53.80% ($n = 87.66$) and 69.11% ($n = 175.83$) from 2001 to 2006. The median of ranitidine 150mg effervescent tablets (innovator) and ranitidine 300mg effervescent tablets (innovator) decreased respectively from 2001 ($n = 20$) to 2006 ($n = 15$) and from 2001 ($n = 30$) to 2006 ($n = 15$) (refer to table 5.39 to table 5.43).

The PDD of ranitidine 75mg effervescent tablets (innovator) decreased with 41.06% ($n = 42.95$) from 2004 to 2005 (table 5.44).

According to table 5.44 it appears that the PDD for most the active ingredients of H₂RAs and PPIs remained stable during the study years. However, it appears that the PDDs of the PPIs' active ingredients were more constant than the PDDs of the H₂RAs' active ingredients. The median for the different PPI active ingredients was reasonably more constant than the median

for the different H₂RA active ingredients (refer to table 5.39 to table 5.43). Thus the changes between the PDD's of H₂RA active ingredients might be explained by the variation in the median. However, these aspects were not further investigated.

5.8.2 THE AVERAGE COST PER DAY OF ACID REDUCING MEDICINE ITEMS

In the following section the estimated average cost per day for histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) was calculated. The average cost was determined for innovator and generic items for each active ingredient and strength.

In this study the average cost per prescription (per month) of each active ingredient was used to calculate the average cost per day. The average cost per day was determined by using the following two methods: by dividing the average cost per prescription (per month) by twenty-eight (for the purpose of this study it was assumed that a month consists of twenty eight days) or by dividing the average cost per prescription (per month) by the median (refer to section 4.7.3.5). The median represents the number of days up to 50% of the study population (refer to section 4.4) received the relevant medicine item (active ingredient and strength). The fact that both twenty-eight days as well as the median were used in determining the average cost per day provides a range where the average cost per day falls in.

The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

In a few cases where the median was sixty capsules/tablets it was assumed that the dosage was twice daily. Therefore in these cases the average cost per prescription (per month) was divided by fifty six instead of twenty eight.

Table 5.45 to table 5.54 provides the average cost per day for H₂RA's and PPI's active ingredients, according to innovator and generic medicine items, during the five study years.

Table 5.45: The average cost (R) per day for cimetidine containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Cimetidine 200mg	28	6.07	2.73	3.23	2.33	4.13	1.23	2.84	0.70	-	0.77
	Median	5.87	2.55	3.02	2.17	5.18	1.15	3.98	0.65	-	0.72
Cimetidine 400mg	28	9.80	6.51	8.79	6.44	7.91	2.87	2.12	1.06	12.17	1.13
	Median	9.15	6.07	8.21	6.01	7.39	2.68	1.98	0.98	11.35	1.05

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.46: The average cost (R) per day for nizatidine containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Nizatidine 150mg	28	8.71	-	8.86	-	7.92	-	6.24	-	4.32	-
	Median	17.42	-	8.86	-	15.84	-	12.48	-	8.63	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.47: The average cost (R) per day for ranitidine containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Ranitidine 75mg	28	2.99	2.45	2.86	2.26	2.24	1.43	2.26	1.04	2.64	0.93
	Median	5.58	5.74	5.73	5.27	6.29	3.33	6.34	2.43	5.92	2.18
Ranitidine 150mg	28	8.57	6.06	8.91	5.73	11.41	2.75	10.79	1.81	14.38	2.15
	Median	8.00	5.66	8.32	5.35	10.65	2.57	10.07	1.69	7.18	2.10
Ranitidine 300mg	28	11.17	7.89	13.07	6.28	18.08	3.80	21.49	1.68	19.58	1.79
	Median	10.43	7.36	12.19	5.86	16.87	3.54	20.06	1.56	18.28	1.67
Ranitidine eff 75mg	28	-	-	-	-	2.24	-	2.50	-	3.57	-
	Median	-	-	-	-	5.23	-	2.92	-	4.16	-
Ranitidine eff 150mg	28	5.68	-	7.12	-	9.29	-	10.02	-	10.20	-
	Median	7.95	-	13.28	-	17.34	-	18.70	-	18.97	-
Ranitidine eff 300mg	28	15.26	-	15.32	-	17.77	-	18.10	-	16.87	-
	Median	14.24	-	14.30	-	16.59	-	16.89	-	31.49	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.48: The average cost (R) per day for famotidine containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Famotidine 20mg	28	9.14	-	4.21	-	-	-	-	-	-	-
	Median	9.14	-	11.22	-	-	-	-	-	-	-
Famotidine 40mg	28	21.50	-	16.45	-	17.31	-	-	-	-	-
	Median	21.50	-	16.45	-	23.08	-	-	-	-	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.49: The average cost (R) per day for esomeprazole containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Esomeprazole 20mg	28	-	-	10.00	-	8.58	-	8.37	-	10.29	-
	Median	-	-	10.00	-	8.58	-	8.37	-	10.29	-
Esomeprazole 40mg	28	-	-	13.15	-	11.83	-	11.80	-	15.34	-
	Median	-	-	26.30	-	11.83	-	11.80	-	15.34	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.50: The average cost (R) per day for omeprazole containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Omeprazole 10mg	28	10.22	7.53	10.82	7.79	9.55	4.33	7.52	4.46	6.94	4.86
	Median	10.22	7.02	10.82	7.27	9.55	4.04	7.52	4.17	6.94	4.86
Omeprazole 20mg	28	14.76	10.89	15.63	11.02	14.97	4.05	11.61	4.19	13.54	5.35
	Median	14.76	14.53	15.63	10.29	14.97	4.05	11.61	4.19	13.54	5.35
Omeprazole 40mg	28	22.52	-	26.36	-	26.54	-	30.13	-	30.18	7.48
	Median	45.04	-	52.73	-	26.54	-	30.13	-	30.18	9.97

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.51: The average cost (R) per day for omeprazole/amoxicillin/clarithromycin containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Omeprazole 20mg/ amoxicillin/ clarithromycin	28	24.24	-	26.44	-	24.17	-	21.78	-	-	-
	Median	13.85	-	15.11	-	13.81	-	12.45	-	-	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.52: The average cost (R) per day for pantoprazole containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Pantoprazole 20mg	28	8.91	-	9.02	-	7.23	-	6.63	-	7.14	6.58
	Median	8.91	-	9.02	-	7.23	-	6.63	-	7.14	6.58
Pantoprazole 40mg	28	13.71	-	14.50	-	12.01	-	11.74	-	13.00	11.45
	Median	13.71	-	14.50	-	12.01	-	11.74	-	13.00	11.45

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.53: The average cost (R) per day for rabeprazole containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Rabeprazole 10mg	28	8.34	-	10.29	-	8.11	-	8.81	-	10.46	-
	Median	8.34	-	10.29	-	8.11	-	8.81	-	10.46	-
Rabeprazole 20mg	28	11.38	-	13.64	-	13.45	-	15.10	-	16.75	-
	Median	11.38	-	13.64	-	13.45	-	15.10	-	16.75	-

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Table 5.54: The average cost (R) per day for lansoprazole containing medicine items, according to innovator and generic medicine items, during 2001, 2002, 2004, 2005 and 2006.

Active ingredient	Number of days	2001		2002		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic	Innovator	Generic
Lansoprazole 15mg	28	10.26	-	11.71	-	9.96	-	9.32	4.13	9.95	2.96
	Median	10.26	-	11.71	-	9.96	-	9.32	3.86	9.95	2.76
Lansoprazole 30mg	28	14.23	-	15.90	-	13.82	-	14.82	4.81	14.06	3.86
	Median	14.23	-	15.90	-	13.82	-	14.82	4.49	14.06	3.61

The average cost per day – The average cost per prescription (per month) divided by the number of days. The average cost per day was calculated by using the average cost per prescription (per month) and the median from table 5.39 to table 5.43.

Ranitidine bismuth citrate was present on the medicine claims database only during 2002 (refer to section 5.5.3.1). The average cost per day of ranitidine bismuth citrate during 2002 was R10.29 per day (refer to table 5.40).

Table 5.45 shows that the average cost per day of innovator medicine items, containing cimetidine, was higher than the average cost per day of generic medicine items. There were no innovator medicine items (tablets), containing cimetidine 200mg, present on this medicine claims database during 2006 (refer to appendix B, table B5). The difference between the average cost per day of innovator and generic medicine items, containing cimetidine 400mg, was respectively R11.04 and R10.30 when the average cost per prescription (per month) was divided by twenty-eight days and the median, during 2006. The median in this case was 30 days (refer to table 5.43).

Table 5.46 shows that the range of the average cost per day for medicine items, containing nizatidine 150mg, was wider than for example the range of the average cost per day for innovator medicine items containing cimetidine 200mg, during the study years. This trend might be explained by the difference between the assumed twenty-eight days and the median ($n = 14$) (refer to table 5.39 to table 5.43).

Table 5.47 shows that the average cost per day of generic medicine items, containing ranitidine 75mg, was higher than the average cost per day of innovator medicine items, containing ranitidine 75mg, during 2001 (when the average cost per prescription (per month) was divided by the median). This trend might be explained by the fact that the median of innovator and generic medicine items differ. The median of innovator and generic medicine items, containing ranitidine 75mg, presented as 15 and 12 respectively during 2001 (refer to table 5.39).

During 2002 there was a wide range of the average cost per day for innovator medicine items, containing esomeprazole 40mg (table 5.49). This might be due to the difference between the assumed twenty-eight days and the median ($n = 14$) (refer to table 5.40).

It appears that the average cost per day of innovator medicine items, containing omeprazole, was higher than the average cost per day of generic medicine items (table 5.50). The average cost per day of innovator medicine items, containing omeprazole 40mg, was similar between 2005 and 2006. This might be explained by the average cost per prescription (per month). The average cost per prescription (per month) for innovator medicine items, containing omeprazole 40mg, increased from 2005 ($R843.63 \pm 292.91$) to 2006 ($R845.01 \pm 284.88$) (refer to table 5.42 and table 5.43).

Summary

The highest average cost per day of all the H₂RAs' and PPIs' active ingredients, was for innovator medicine items, containing omeprazole 40mg, during 2004 (n = R26.54), 2005 (n = R30.13) and 2006 (n = R30.18). While the highest average cost per day of all the H₂RAs' and PPIs' active ingredients, was for innovator medicine items, containing omeprazole/amoxicillin/clarithromycin, during 2001 (n = R24.24) and 2002 (n = R26.44) (table 5.45 to table 5.54).

It appears that the trend was that the average cost per day of innovator medicine items was higher than the average cost per day of generic medicine items (table 5.45 to table 5.54). This might be explained by a lower average cost for generic medicine items.

5.9 SUMMARY

In this chapter the results of the empirical investigation have been discussed. The focus was mainly on the cost and utilisation of acid reducing medicine items with special reference to histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs). The influence of the new pricing regulations on the cost of acid reducers was investigated.

CHAPTER 6:

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

In this chapter the conclusions of the study, based on the results of the literature review and the empirical investigation, will be discussed. Limitations encountered during the study will also be discussed and certain recommendations will also be made.

6.2 CONCLUSIONS

The following conclusions can be formulated with regard to the literature review:

The first research objective was to investigate acid-related disorders and their treatment.

This was done through a thorough review of the literature (refer to chapter 2). An overview of acid reducing medicine and acid-related disorders was provided.

It was concluded that acid-related disorders are a common problem that reduces the patients' quality of life and include the following disorders: dyspepsia, gastroesophageal reflux disease (GORD), benign peptic ulcers of the stomach and duodenum, ulcers secondary to the use of conventional non-steroidal anti-inflammatory drugs (NSAIDs), and ulcers due to Zollinger-Ellison syndrome (Hoogerwerf & Pasricha, 2001:1005). The current clinical practice with regard to these disorders was discussed. The treatments of these disorders consist of life-style modifications and medicine treatment including over-the-counter (OTC) antacid, histamine-2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs). The literature study has shown PPIs to be the therapy of choice. Since the initial choice of treatment has a long-term impact on outcomes as well as long-term cost implications, economic evaluations of competing strategies are in demand.

Finally it was concluded that treatment for *H.pylori* should be initiated with a PPI-based three-drug regimen (see Table 2.6). PPI-based three-drug regimen is most efficient, better tolerated, simpler and also associated with better adherence (Dipiro, 2003a:270).

The second research objective was to conceptualise what managed health care, pharmacoeconomics and drug utilisation entail, with special reference to acid reducing medicine.

This was done through a literature review (refer to chapter 3). A brief overview of the nature and structure of managed health care was given. Drug utilisation review (DUR) and pharmaco-

economics were defined, classified and discussed. The changes that influence the South African health care system were discussed. These changes included generic substitution and the new pricing legislation. Examples of pharmaco-economic studies as related to acid-related disorders were provided to conceptualise the implementation of these tools as an aid for decision making in health care management.

It was concluded that health care providers no longer make treatment decisions independent of the consideration of cost. Therefore the treatment provided must not only provide value but the value must be documented to justify spending money. For example a cost-effectiveness analysis (CEA) found that treating healed GORD with maintenance PPI from the beginning is the most effective and most costly approach (Harris *et al.*, 1997:85). While a study conducted by Ofman *et al.* (2000:906) concluded that the management of oesophagitis with rabeprazole is more effective and may be more cost effective than management with generic ranitidine, despite rabeprazole's higher per-unit cost.

The following conclusions can be formulated with regard to the empirical investigation:

*The **third research objective** was to investigate the possible differences in the utilisation patterns and/or cost, before and after the implementation of the pricing regulations in 2004.*

The third research objective was investigated in collaboration with the following research objectives: research objectives four, five, six and seven.

*The **fourth research objective** was to investigate the prevalence and prescribing patterns of medicine items in general, as well as the costs associated with these medicine items.*

The total number of prescriptions claimed (refer to table 5.1), the total number of medicine items prescribed (refer to table 5.1.2) as well as the total cost of medicine items (refer to table 5.1.4) increased from 2001 to 2004 and decreased from 2004 to 2006. There was an increase of 8.71% (n = R22.43) in the average cost per prescription on the total database from 2001 to 2006 (refer to table 5.1.3), while the average cost per medicine items decreased with 8.47% (n = R10.90) for the total database from 2001 to 2006 (refer to table 5.1.5).

The decrease in the prevalence might be explained by a number of factors namely a change in the number and profile of the medical scheme claims, medical scheme members as well as changes in the treatment patterns of acid-related disorders. The reduction in the cost of medicine items could be the result of the implementation of the new pricing regulation within 2004 (refer to section 3.5.3) as well as an increase in the use and availability of generic items (refer to section 3.5.1).

*The **fifth research objective** was to investigate the prevalence and prescribing patterns of gastro-intestinal tract (GIT) medicine items, as well as the costs associated with these medicine items.*

The number of prescriptions containing at least one GIT (refer to table 5.1.1) as well as the number of GIT medicine items (refer to table 5.1.2) increased from 2001 to 2004 and then decreased from 2004 to 2006. The same trend was observed with regard to the total cost of GIT medicine items (refer to table 5.1.4). There was a decrease of 17.85% (n = R34.51) in the average cost per GIT prescription from 2001 to 2006 (refer to table 5.1.3). However, the average cost per GIT medicine item decreased with 20.51% (n = R32.61) from 2001 to 2006 (refer to table 5.1.5).

As previously explained the decrease in the prevalence might be explained by a number of factors namely a change in the number and profile of the medical scheme claims, medical scheme members as well as changes in the treatment patterns of acid-related disorders. The reduction in the cost of medicine items could be the result of the implementation of the new pricing regulation within 2004 (refer to section 3.5.3) as well as an increase in the use and availability of generic items (refer to section 3.5.1).

*The **sixth research objective** was to analyse the prescription patterns of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.*

The prevalence percentage of acid reducers decreased from 2.74% in 2001 to 2.50% in 2006 (table 5.1.2). The cost percentage that acid reducers contributed to the total cost of all medicine items claimed decreased from 4.89% in 2001 to 3.72% in 2006 (table 5.1.4).

The average cost per acid reducing medicine item was higher than the average cost per medicine item on the total database (table 5.1.5). This might indicate that acid reducers are relatively expensive products. However, it was not practical significant proof that acid reducers were in fact more expensive. Therefore the CPI (refer to section 4.6.4) was used as another measuring tool. Most of the PPIs had CPI > 1, which indicated that PPIs were relatively expensive products. Since PPIs represented more than 50% of acid reducing medicine items claimed (table 5.2.1), it might be concluded that acid reducers are relatively expensive.

The average cost per acid reducer increased with 5.35% from 2001 to 2002 and then decreased with 15.23% from 2002 to 2004 and again with 15.05% from 2004 to 2006 (table 5.1.5). However, the changes in the average cost of acid reducers was of no practical significance (table 5.1.5.1). The average cost per acid reducer prescription decreased with 23.50% (n = R60.42) from 2001 to 2006 (table 5.1.3).

In conclusion a decreasing trend was observed from 2001 to 2006 with regard to the contribution of acid reducers to the total number of medicine items claimed and the total cost. This decrease in prevalence could be explained by combinations of factors namely a change in the number and profile of the medical scheme members as well as a change in the treatment pattern of acid-related disorders. The decrease in the cost of acid reducers could be the result of the implementation of legislation on generic substitution (refer to section 3.5.1), the transparent pricing regulations (refer to section 3.5.3) and the availability of more generic medicine items on the South African market.

*The **seventh research objective** was to analyse the prescription patterns for different types (sub-pharmacological groups) of acid reducing medicine in South Africa, as well as the costs associated with these medicine items.*

PPIs formed the sub-pharmacological group most often prescribed during the study years. The prevalence percentage for PPIs stayed relatively constant for the duration of this study. PPIs contributed to approximately 50% of all acid reducers claimed (table 5.2.1).

According to The Medicines and Related Substances Act (Act 101 of 1965 as amended) medicine items from schedule 3 and upwards can only be claimed from the medical aid if the patient is in possession of a valid prescription. Since antacids are normally unscheduled, schedule 0 or schedule 2, antacids might be claimed without a valid prescription if the medical scheme allowed it. Antacids continued to be the second most prescribed sub-pharmacological group. As noted earlier in this study this observation might be due to the fact that most patients who experienced frequent acid-related symptoms do not necessarily seek professional medical care and very often use antacids as self-medication (refer to section 5.5.2.2).

The prevalence percentage of H₂RAs increased with 2.65% from 2001 to 2006 (table 5.2.1). A limitation of this study was that data for this analysis were obtained from one medicine claims database (refer to chapter 6). Thus the results could only be generalised to the specific database used and to the specific study population. This database also includes only medication that was prescribed and claimed through a medical scheme. Therefore medicine items paid for by the patients themselves were not included in the database.

The PPIs consistently contributed to more than 70% of the total cost of all acid reducing medicine items during the five study years (table 5.2.2).

There was a decrease of 5.82% in the percentage cost contributed by PPIs to the total cost of acid reducers from 2001 to 2006 (table 5.2.2). Interestingly there was an increase of 5.12% in

the percentage cost that H₂RAs represented of the total cost of acid reducers from 2001 to 2006 (table 5.2.2).

The average cost per PPI medicine item decreased with 32.70% from 2001 to 2006 (table 5.2.3). While the average cost per H₂RA medicine item decreased with 8.49% from 2001 to 2006 (table 5.2.3). The decrease in the average cost of H₂RAs and PPIs respectively were not of practical significance (table 5.2.3). The large difference between the declines observed with regard to the average cost per PPI medicine items might be explained by the introduction of generic medicine items to the market. During 2001 a number of generic medicine items were already available for H₂RA medicine items, while generic medicine items for most of the PPIs became available only during 2004 to 2006.

*The **eighth research objective** was to determine the prevalence of acid reducing medicine items according to trade name and active ingredients.*

Figure 5.2 reveals that lansoprazole was the active ingredient most often prescribed during 2001 and 2002. Esomeprazole was the active ingredient with the highest prevalence for 2004. Omeprazole was the active ingredient with the highest prevalence in 2005 and 2006. Lanzor[®] 30mg was the acid reducer with the highest cost from 2001 to 2005, while Pariet[®] 20mg took the lead in 2006 (table 5.9). Table 5.19 shows that Zantac[®] 150mg effervescent tablets constituted the H₂RA, with the highest total cost, during the five study years.

*The **ninth research objective** was to analyse the prescribing patterns for individual acid reducing medicine items in South Africa, as well as the costs associated with these medicine items.*

Table 5.19 shows that Zantac[®] 150mg effervescent tablets ranked as the H₂RA, with the highest total cost, during all five study years. Zantac[®] 300mg effervescent tablets presented as the H₂RA, with the second highest total cost, from 2004 to 2006. Ranihexal[®] 150mg appeared among the top five of H₂RAs although it had a CPI < 1 for all five study years.

The top five PPI products, according to cost, stayed reasonably the same from 2001 to 2006 (Table 5.31). Lanzor[®] 30mg capsules remained the PPI with the highest cost from 2001 to 2005. During 2006 Pariet[®] 20mg tablets proved to be the PPI with the highest cost.

*The **tenth research objective** was to determine the influence of generic substitution on the cost and prescribing patterns of acid reducing medicine.*

Figure 5.6 shows that there was a steady increase in the percentage of generic antacids claimed (refer to appendix E). The percentage generic H₂RAs claimed increased from 2001 to

2004 and decreased from 2005 to 2006. The percentage of generic PPIs claimed increased from 2001 to 2002, decreased from 2002 to 2004 and increased from 2004 to 2006. There were no generic medicine items available for the cytoprotective agents during the study years.

New legislation on generic medicine came into effect on 2 May 2003. This new legislation compelled the pharmacist to inform all patients of the benefits of generic substitution. Therefore it may be expected that the percentage innovator medicine items claimed decreased through the study years. However, the percentage acid reducing innovator items claimed decreased with 4.50% from 2001 to 2002, increased with 1.01% from 2002 to 2004 and decreased with 31.06% from 2004 to 2006. The increase in the percentage innovator acid reducing medicine items claimed from 2002 to 2004 might be explained by the introduction of Nexiam® (esomeprazole) into the market during 2002. The prevalence percentage of esomeprazole increased with 8.72% from 2002 to 2004 (refer Appendix A) and esomeprazole was the active ingredient most often prescribed during 2004. As mentioned above the results of this study reveal that acid reducers were relatively expensive medications. The drastic decrease in the percentage innovator medicine items claimed from 2004 and 2006 might be explained by the following argument. In 2004 a considerable number of generic PPI products were available on the market. The average cost of innovator and generic acid reducing medicine items decreased with practical significance ($d = 0.81$) from 2001 to 2005 (refer to section 5.6.1.2). This implies that the generic medicine items were cheaper than the innovator medicine items (in the case of the PPIs). It seems that the consumer would prefer the cheaper generic medicine item probably encouraged by the limitations placed by medical aid on the reimbursement that they are prepared to pay via the introduction of a reference medicine pay system.

The influence of generic substitution on the cost of acid reducing medicine items was revealed by the following research objectives: four, five, six and seven.

*The **eleventh research objective** was to determine the prevalence and cost of combinations (proton pump inhibitors (PPIs)) prescribed together with amoxicillin, bismuth, clarithromycin, metronidazole and tetracycline on one prescription) used in the treatment of Helicobacter pylori.*

Table 5.38 shows that the prevalence of the two-drug regimens was the highest during the five study years. The *H.pylori* eradication treatments, which included different antibiotics, increased from 2.72% in 2001 to 5.05% in 2006.

*The **twelfth research objective** was to determine the prescribed daily dose for acid reducing medicine with special reference to histamine-2 receptor antagonists (H_2 RAs) and proton pump inhibitors (PPIs) according to active ingredient, strength and innovator or generic medicine item.*

Table 5.44 shows that the PDD for most of the active ingredients of H₂RAs and PPIs during the study years remained stable. However, it appears that the PDDs of the PPIs' active ingredients were more constant than the PDDs of the H₂RAs' active ingredients. The median of the different PPI active ingredients was reasonably more constant than the median of the different H₂RA active ingredients (refer to table 5.39 to table 5.43). Thus the changes between the PDDs of H₂RA active ingredients might be explained by the variation in the median (the number of days the relevant medicine item was claimed for).

It appears that the trend was that the average cost per day of innovator medicine items was higher than the average cost per day of generic medicine items (table 5.45 to table 5.54). This might be explained by a lower average cost for generic medicine items.

6.3 LIMITATIONS AND SHORTCOMINGS OF THIS STUDY

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

- All the data concerning medicine prescribing patterns and the cost of medicine usage obtained from the database after refinement were considered accurate and correct.
- Due to the unavailability of the data of 2003, the prescribing patterns and costs associated with this period cannot be compared with the other periods.
- Data for the analysis were obtained from one medicine claims database, thus, limiting external validity, implying that results can be generalised only to the specific database used, as well as to the specific study populations.
- No clinical data (diagnoses) were available on the database; therefore the relevance of some of the prescribing patterns could not be determined.
- No demographic data, such as age, gender and race were available on the database.
- Compliance could not be determined.
- As related to the prescribed period certain assumptions were made.

6.4 RECOMMENDATIONS

The following recommendations can be made after the completion of this study:

- A data system must be developed to monitor (in general) the prescribing patterns of acid reducing medicine on a continuing base.

- More than one medicine claims database should be used to analyse prevalence and cost with reference to acid reducing medicine.
- The usage patterns of histamine-2 receptor antagonists (H₂RAs) as prescribed and self-medication should be further investigated.
- The cost-saving due to generic substitution should be further investigated, including cost aspects.
- Possible drug-drug interactions between acid reducing medicines should be analysed.

6.5 SUMMARY

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

BIBLIOGRAPHY

ALLESCHER, H.D. 2006. Functional dyspepsia – a multicausal disease and its therapy. *Phytomedicine*, 31:2-11.

ALTMAN, D.F. 2001. Drugs used in gastrointestinal diseases. (*In* Katzung, B.G., ed. Basic & clinical pharmacology. 8th ed. New York: McGraw-Hill. p.1064-1076.)

ANDERSSON, K. & CARLSSON, E. 2005. Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. *Pharmacology and therapeutics*, 108:294-307.

ANELL, A. & SVARVAR, P. 2000. Pharmaco-economics and clinical practice guidelines: a survey of attitudes in Swedish formulary committees. *Pharmaco-economics*, 17:175-185.

ARGUEDAS, M.R., HEUDEBERT, G.R., KLAPOW, J.C., CENTOR, R.M., ELOUBEIDI, M.A., WILCOX, C.M., SPECHLER, S.J. & VA COOPERATIVE STUDY GROUP. 2004. Re-examination of the cost-effectiveness of surgical versus medical therapy in patients with gastroesophageal reflux disease: the value of long-term data collection. *American journal of gastroenterology*, 99:1023-1028.

ARMSTRONG, D. 1996. *Helicobacter pylori* infection and dyspepsia. *Scandinavian journal of gastroenterology*, 31:38-47.

ARMSTRONG, D. 2005. Gastroesophageal reflux disease. *Current opinion in pharmacology*, 5:589-595.

BATE, C.M., RILEY, S.A., CHAPMAN, R.W.G., DURNIN, A.T. & TAYLOR, M.D. 1999. Evaluation of omeprazole as a cost effective diagnostic test for gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics*, 13:59-66.

BEERS, M.H. & BERKOW, R., eds. 2004. The Merck manual of diagnosis and therapy. 17th ed. Whitehouse station, N.J.: Merck Research Laboratories. 2833p.

BERNERSEN, B., JOHNSEN, R. & STRAUME, B. 1996. Non-ulcer dyspepsia and peptic ulcer: the distribution in a population and their relation to risk factors. *Gut*, 38:822-825.

BESTER, M. & HAMMANN, E. 2005. Mediscor medicines review: 2004.
http://www.mediscor.net/pages/pmb/pmb_main.htm Date of access: 17 Sep. 2007.

BESTER, M., BREWS, M. & HAMMANN, E. 2006. Mediscor medicines review: 2005.
http://www.mediscor.net/pages/pmb/pmb_main.htm Date of access: 17 Sep. 2007.

BOARD OF HEALTH CARE FUNDERS. 2006. New dispensing fees are good for you, says BHF. http://www.persfin.co.za/general/print_article.php?fArticleId=3520663&fSectionId=7 Date of access: 15 Nov. 2006.

BONK, R.J. 1999. Pharmacoeconomics in perspective: a primer on research techniques and information. New York: Pharmaceutical Products Press. 116p.

BOOTMAN, J.L., TOWNSEND, R.J. & MCGHAN, W.F., eds. 1991. Introduction to pharmacoeconomics. (In Bootman, J.L., Townsend, R.J. & McGhan, W.F., eds. Principles of pharmacoeconomics. Cincinnati, OH. : Harvey Whitney Books. p. 2-17.)

BYRNE, M.F. & MURRAY, F.E. 1999. Formulary management of proton pump inhibitors. *Pharmacoeconomics*, 16:225-246.

BYTZER, P. 2003. Goals of therapy and guidelines for treatment success in symptomatic gastroesophageal reflux disease patients. *American journal of gastroenterology*, 98:S31-S39.

CARO, J.J., SALAS, M. & WARD, A. 2001. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole and pantoprazole compared with omeprazole, ranitidine and placebo: evidence from randomized clinical trials. *Clinical therapeutics*, 23:998-1017.

CDER see **UNITED STATES. FOOD AND DRUG ADMINISTRATION.**

CLOUSE, J. 2002. Establishing value in managed care: cost-effectiveness or budgetary impact? *Journal of allergy and clinical immunology*, 109:S511-S514.

DAVEY, P.G., MALEK, M., DODD, T. & MACDONALD, T. 1997. Pharmacoeconomics and drug prescribing. (In Speight, T.M. & Holford, N.H.G., ed. Avery's drug treatment. 4th ed. Auckland: Adis. p. 394-422.)

DELANEY, B.C., WILSON, S., ROALFE, A., ROBERTS, L., REDMAN, V., WEARN, A., BRIGGS, A. & HOBBS, F.D.R. 2000. Cost effectiveness of initial endoscopy for dyspepsia in patients over age 50 years: randomised controlled trial in primary care. *Lancet*, 356:1965-1969.

DENT, J., JONES, R., KAHRILAS, P. & TALLEY, N.J. 2001. Management of gastroesophageal reflux disease in general practice. *British medical journal*, 322:344-347.

DEVAULT, K.R. & CASTEL, D.O. 1999. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *American journal of gastroenterology*, 94:1434-1442.

DIPIRO, J.T. 2003a. Peptic ulcer disease. (*In* Wells, B.G., Dipiro, J.T., Schwinghammer, T.L. & Hamilton, C.W., eds. *Pharmacotherapy handbook*. 5th ed. New York: McGraw-Hill. p.268-273.)

DIPIRO, J.T. 2003b. Gastroesophageal reflux disease. (*In* Wells, B.G., Dipiro, J.T., Schwinghammer, T.L. & Hamilton, C.W., eds. *Pharmacotherapy handbook*. 5th ed. New York: McGraw-Hill. p.216-224.)

DOMAGALA, F., FICHEUX, H., HOUIN, G. & BARRÉ, J. 2006. Pharmacokinetics of tenatropazole, a newly synthesized proton pump inhibitor, in healthy male Caucasian volunteers. *Arzneimittel-Forschung*, 56: 33-39.

DORE, M.P., GRAHAM, D.Y., MELE, R., MARRAS, L., NIEDDU, S., MANCA, A. & REALDI, G. 2002. Colloidal bismuth subcitrate-based twice-a-day quadruple therapy as primary or salvage therapy for *Helicobacter pylori* infections. *American journal of gastroenterology*, 97:857-860.

DU TOIT, J. 2003. Generic substitution by pharmacists. *Pharmaciae*, 11:4.

ELLIS, C.N., REITER, K.L., WHEELER, J.R.C., FENDRICK, A.M. & MICHIGAN, A.A. 2002. Economic analysis in dermatology. *Journal of the American Academy of Dermatology*, 46:271-283.

ERSTAD, B.L. 2004. Cost-effectiveness of proton pump inhibitor therapy for acute peptic ulcer-related bleeding. *Critical care medicine*, 32:1277-1283.

ERWIN, W.G. 1991. The definition of drug utilization review: statement of issues. *Clinical pharmacology & therapeutics*, 50:596-599.

EVERITT, B.S. 1998. *The Cambridge dictionary of statistics*. Cambridge: Cambridge University Press. 360p.

FAIRFIELD, G., HUNTER, D.J., MECHANIC, D. & ROSLEFF, F. 1997. Managed care: origins, principles and evolution. *BMJ*, 314:1823.
<http://www.bmj.com/cgi/content/full/314/7079/1823?maxtoshow=&HITS=10&hits=10&RESULTF>
Date of access: 11 Nov. 2006.

FARMER, C.M. 2001. The usage of proton pump inhibitors: a pharmaco-economic perspective. Potchefstroom : PU for CHE. (Dissertation – M.Pharm.) 226 p.

FASS, R., OFMAN, J.J., GRALNEK, I.M., JOHNSON, C., CAMARGO, E., SAMPLINER, R.E. & FENNERTY, B. 1999. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Archives of internal medicine*, 159:2161-2168.

FREUND, D.A. & DITTUS, R.S. 1992. Principles of pharmaco-economic analysis of drug therapy. *Pharmaco-economics*, 1:20-32.

FREVEL, M., DAAKE, H., JANISCH, H.D., KELLNER, H.U., KREZDORN, H.G., TANNEBERGER, D. & WACK, R. 2000. Eradication of *Helicobacter pylori* with pantoprazole and two antibiotics: a comparison of two short-term regimens. *Alimentary pharmacology & therapeutics*, 14:1151-1157.

GALMICHE, J.P., BRULEY DES VARANNES, S., DUCROTTÉ, P., SACHER-HAVELIN, S., VAVASSEUR, F., TACCOEN, A., FIORENTINI, P. & HOMERIN, M. 2004. Tenatoprazole, a novel proton pump inhibitor with a prolonged plasma half-life: effects on intragastric pH and comparison with esomeprazole in healthy volunteers. *Alimentary pharmacology & therapeutics*, 19: 655-662.

GIBBON, C.J., ed. 2003. South African medicines formulary. 6th ed. Cape Town: The South African Medical Association. 569p.

GISBERT, J.P., KHORRAMI, S., CARBALLO, F., CALVET, X., GENE, E. & DOMINGUEZ-MUNOZ, E. 2004. Meta-analysis: *Helicobacter pylori* eradication therapy vs. antisecretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer. *Alimentary pharmacology & therapeutics*, 19:617-629.

GOEREE, R., O'BRIEN, B.J., BLACKHOUSE, G., MARSHALL, J., BRIGGS, A. & LAD, R. 2002. Cost-effectiveness and cost-utility of long-term management strategies for heartburn. *Value in health*, 5:312-324.

GRABOWSKI, H. & MULLINS, C.D. 1997. Pharmacy benefit management, cost-effectiveness analysis and drug formulary decisions. *Social science and medicine*, 45:535-544.

GREENWALD, D.A. 2004. Aging, the gastrointestinal tract, and risk of acid-related disease. *The American journal of medicine*, 117:8S-19S.

GUO, J.J., GIBSON, J.T. & BARKER, K.N. 1996. Economic evaluation of drug utilization review on medicaid pharmacy dispensing behavior: an empiric marginal analysis. *Clinical therapeutics*, 18:50.

- HARRIS, R.A., KUPPERMANN, M. & RICHTER, J.E.** 1997. Prevention of recurrence of erosive reflux esophagitis: a cost-effectiveness analysis of maintenance proton pump inhibition. *The American journal of medicine*, 102:78-88.
- HEUDEBERT, G.R., CENTOR, R.M., KLAPOW, J.C., MARKS, R., JOHNSON, L. & WILCOX, C.M.** 2000. What is heartburn worth? A cost-utility analysis of management strategies. *Journal of general internal medicine*, 15:175-182.
- HOLTMANN, G., MALDONADO-LOPEZ, E. & HAAG, S.** 2004. Heartburn in primary care: problems below the surface. *Journal of gastroenterology*, 39:1027-1034.
- HOOPERWERF, W.A. & PASRICHA, P.J.** 2001. Agents used for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease. (*In* Hardman, J.G. & Limbird, L.E., eds. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York, : McGraw-Hill. p.1005-1020.)
- HOWDEN, C.W. & HUNT, R.H.** 1998. Guidelines for the management of *Helicobacter pylori* infections. *American journal of gastroenterology*, 93: 2330-2338.
- HUGHES, D.A., BODGER, K., BYTZER, P., DE HERDT, D. & DUBOIS, D.** 2005. Economic analysis of on-demand maintenance therapy with proton pump inhibitors in patients with non-erosive reflux disease. *Pharmaco-economics*, 23:1031-1041.
- HUNGIN, A.P.S. & RUBIN, G.** 1999. Long-term proton pump inhibitors in general practice. *British journal of general practice*, 49:451-453.
- IACOPINI, F., CRISPINO, P., PAOLUZI, O.A., CONSOLAZIO, A., PICA, R., RIVERA, M., PALLADINI, D., NARDI, F. & PAOLUZI, P.** 2005. One-week once-daily triple therapy with esomeprazole, levofloxacin and azithromycin compared to a standard therapy for *Helicobacter pylori* eradication. *Digestive and liver diseases*, 37:571-576. Available: ScienceDirect.
- IGLEHART, J.K.** 1994. Physicians and the growth of managed care: health policy report. *New England journal of medicine*, 331:1167-1171.
- INDOMI, J.M.** 2002. On-demand and intermittent therapy for gastro-oesophageal reflux disease: economic considerations. *Pharmaco-economics*, 20:565-576.
- INDOMI, J.M., JAMAL, R., MURATA, G.H., HOFFMAN, R.M., LAVEZO, L.A., VIGIL, J.M., SWANSON, K.M. & SONNENBERG, A.** 2001. Step-down management of gastroesophageal reflux disease. *Gastroenterology*, 121:1095-1100.

- JAISINGH, L.R.** 2000. Statistics for the utterly confused. New York: McGraw-Hill. 318p.
- JASANI, K., PITERMAN, L. & McCALL, L.** 1999. Gastroesophageal reflux and quality of life: patients' knowledge, attitude and perceptions. *Australian family physician*, 28:S15-S18.
- JOLICOEUR, L.M., JONES-GRIZZLE, A.J. & BOYER, J.G.** 1992. Guidelines for performing a pharmaco-economic analysis. *American journal of hospital pharmacy*, 49:1741-1747.
- JONES, J.K.** 1991. A view from the drug utilization review management organization sector. *Clinical pharmacology and therapeutics*, 50:620-625.
- JONES, J.S.** 2006. Pharmaco-economics in South Africa. *South African medical journal*, 96:96.
- JONES, R.H., LYDEARD, S.E., HOBBS, F.D.R., KENKRE, J.E., WILLIAMS, E.I., JONES, S.J., REPPER, J.A., CALDOW, J.L., DUNWOODIE, W.M.B. & BOTTOMLEY, J.M.** 1990. Dyspepsia in England and Scotland. *Gut*, 31:401-405.
- KATZUNG, B.G. & JULIUS, D.J.** 2001. Histamine, serotonin & the ergot alkaloids. (In Katzung, B.G., ed. Basic & clinical pharmacology. 8th ed. New York: McGraw-Hill. p.265-291.)
- KEE, J.L. & HAYES, E.R.** 2000. Pharmacology: a nursing process approach. 3rd ed. Philadelphia: Saunders. 1032p.
- KELLER, G. & WARRACK, B.** 2000. Statistics for management and economics. 5th ed. Pacific Grove : Duxbury Press. 901p.
- KIEL, J.M.** 2003. Electronic managed care: the utilization of information technology in a managed care environment. *Health care manager*, 22:16-20.
- KIRKWOOD, B.R.** 1988. Essentials of medical statistics. London: Blackwell Science. 234p.
- KIVIOJA, A., LINNOSMAA, I., VEHVILAINEN, A. & VOHLONEN, I.** 2004. Cost-minimization analysis of treatment of gastroesophageal reflux disease: implications of varying holding time on conclusions. *European journal of pharmaceutical sciences*, 21:171-178.
- KUBACKA, R.** 1996. A primer on drug utilization review: using information obtained from drug utilization reviews, pharmacists can make drug therapy more appropriate, effective and cost-efficient. *Journal of the American Pharmaceutical Association*, NS36: 257-261.

KULIG, M., NOCON, M., VIETH, M., LEODOLTER, A., JASPERSEN, D., LABENZ, J., MEYER-SABELLEK, W., STOLTE, M., LIND, T., MALFERTHEINER, P. & WILlich, S.N.

2004. Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. *Journal of clinical epidemiology*, 57:580-589.

LAINE, L., HOPKINS, R.J. & GRIARDI, L.S. 1998. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the united states been overstated? A meta-analysis of rigorously designed trials. *American journal of gastroenterology*, 93:1409-1415.

LEE, D. & BERGMAN, U.L.F. 1994. Studies of drug utilization. (*In* Strom, B.L., ed. *Pharmacoepidemiology*. 2nd ed. Chichester: Wiley. p. 379-393.)

LEONTIADIS, G.I., SHARMA, V.K. & HOWDEN, C.W. 2005. Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. *BMJ*, 330:568.

<http://bjm.com/cgi/content/full/330/7491/568> Date of access: 24 Apr. 2006.

LOCKE, G.R., TALLEY, N.J., FETT, S.L., ZINSMEISTER, A.R. & MELTON, L.J. 1997. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*, 112:1448-1456.

LOGAN, R. & DELANEY, B. 2001. ABC of the upper gastrointestinal tract: implications of dyspepsia for the NHS. *BMJ*, 323:675-677. <http://www.bmj.com/cgi/reprint/323/7314/675> Date of access: 20 Feb. 2006.

MAJUMDAR, S.R., SOUMERAI, S.B., FARRAYE, F.A., LEE, M., KEMP, J.A., HENNING, J.M., SCHRAMMEL, P., LECATES, R.F. & ROSS-DEGNAN, D. 2003. Chronic acid-related disorders are common and underinvestigated. *American journal of gastroenterology*, 98:2409-2414.

MALEK, M.O. 1996. Pharmaco-economics. Part1. Introduction. *Pharmaceutical journal*, 257:759-761.

MARTIN, P. & PIERCE, R. 1994. Practical statistics for the health sciences. Melbourne: Nelson. 274p.

MCCOMBS, J.S. 1998. Pharmaco-economics: what is it and where is it going? *American journal of hypertension*, 11:112S-119S.

McQUAID, K.R. 2004. Alimentary tract. (*In* Tierney, L.M., Mcphee, S.J. & Papadakis, M.A., eds. *Current medical diagnosis & treatment*. 43rd ed. New York: McGraw-Hill. p.515-622.)

MEDICOVER. 2007. Medcover handbook: glossary and other important information.
<http://www.medicover.co.za/content/handbook/glossary.asp> Date of access: 2 Apr. 2007.

MEDIHELP. 2007. Definition list.
<http://www.medihelp.co.za/new/default.asp?currentpage=basemodule&id=20&level=2&subid=159> Date of access: 23 Apr. 2007.

MEDIKREDIT. 2007. Nappi codes and files. <https://www.medikredit.co.za/Nappi/nappi.htm>
Date of access: 2 Apr. 2007.

MEDISCOR. 2007. Prescribed minimum benefits (PMBs).
http://www.mediscor.net/pages/pmb/pmb_main.htm Date of access: 31 May 2007.

MESTERN, A. 2003. Article on generic medicines. *BP Southern Africa Medical Aid Society: newsletter.* http://www.mhg.co.za/SchemeSite/docs/bp/news/november_2003.pdf Date of access: 26 Jul. 2007.

METZ, D.C., FORSMARK, C.E., LEW, E.A., STARR, J.A., SOFFER, E.F., BOCHENEK, W. & PISEGNA, J.R. 2001. Replacement of oral proton pump inhibitors with intravenous pantoprazole to effectively control gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *American journal of gastroenterology*, 96:3274-3280.

METZ, D.C., SOFFER, E., FORSMARK, C.E., CRYER, B., CHEY, W., BOCHENEK, W. & PISEGNA, J.R. 2003. Maintenance oral pantoprazole therapy is effective for patients with Zollinger-Ellison syndrome and idiopathic hypersecretion. *American journal of gastroenterology*, 98:301-307.

MISIEWICZ, J.J., HARRIS, A.W., BARDHAN, K.D., LEVI, S., O'MORAIN, C., COOPER, B.T., KERR, G.D., DIXON, M.F., LANGWORTHY, H., PIPER, D. & LANSOPRAZOLE HELICOBACTER STUDY GROUP. 1997. One week triple therapy for *Helicobacter pylori*: a multicentre comparative study. *Gut*, 41:735-739.
<http://gut.bmjjournals.com/cgi/content/full/41/6/735> Date of access: 19 Sep. 2006.

MOORE, K.L. & DALLEY, A.F. 1999. Clinically oriented anatomy. 4th ed. Philadelphia: Lippincott Williams & Wilkins. 1167 p.

NANDURKAR, S., TALLEY, N.J., XIA, H., MITCHELL, H., HAZEL, S. & JONES, M. 1998. Dyspepsia in the community is linked to smoking and aspirin use but not to *Helicobacter pylori* infection. *Archives of internal medicine*, 158:1427-1433.

NG, T., MAZIAK, D.E. & SHAMJI, F.M. 2001. Esophageal perforation: a rare complication of Zollinger-Ellison syndrome. *Annals of thoracic surgery*, 72:592-593.

O'CONNOR, J.B., PROVENZALE, D. & BRAZER, S. 2000. Economic considerations in the treatment of gastroesophageal reflux disease: a review. *American journal of gastroenterology*, 95:3356-3364.

OFMAN, J.J., DORN, G.H., FENNERTY, M.B. & FASS, R. 2002. The clinical and economic impact of competing management strategies for gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics*, 16:261-273.

OFMAN, J.J., YAMASHITA, B.D., SIDDIQUE, R.M., LARSON, L.R. & WILLIAN, M.K. 2000. Cost effectiveness of rabeprazole versus generic ranitidine for symptom resolution in patients with erosive esophagitis. *American journal of managed care*, 6:905-916.

OLSEN, B.M. 2003. Approaches to pharmacy benefit management and the impact of consumer cost sharing. *Clinical therapeutics*, 25:250-272.

PEURA, D.A., GUDMUNDSON, J., SIEPMAN, N., PILMER, B.L., COLLIS, C.M. & FRESTON, J. 2001. PPIs first-line treatment for dyspepsia. *American journal of gastroenterology*, 96:S65.

PHARMACEUTICAL SOCIETY OF SOUTH AFRICA. 2007. The PSSA – pharmacy in action: update on the dispensing fee process. *PSSA newsletter*: 34.
http://www.pssa.org.za/index_full.asp Date of access: 12 Sep. 2007.

PILLAY, A. 2006. International benchmarking of medicine prices in South Africa.
<http://www.doh.za/search/index.html> Date of access: 5 June 2007.

PILOTTO, A., FRANCESCHI, M., LEANDRO, G., SCARCELLI, C., D'AMBROSIO, L.P., SERIPA, D., PERRI, F., NIRO, V., PARIS, F., ANDRIULLI, A. & DI MARIO, F. 2006. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *Journal of the American Geriatrics Society*, 54:1537-1542.

PORTH, C.M. 1998. Alterations in gastrointestinal functions. (*In* Porth, C.M., ed. Pathophysiology: concepts of altered health states. 5th ed. Philadelphia: Lippincott. p.719-744.)

PRESCRIBING SUPPORT. THE INFORMATION CENTRE. 2007. Defined daily doses and prescribed daily doses. <http://www.ic.nhs.uk/our-services/prescribing-support/measures/ddds-and-pdds> Date of access: 21 Jun. 2007.

PRESCRIPTION PRICING AUTHORITY. 2004. Drugs for dyspepsia.
<http://www.ppa.org.uk/news/pact-082004.htm> Date of access: 8 Feb. 2006.

PSSA. see **PHARMACEUTICAL SOCIETY OF SOUTH AFRICA.**

QUEENBOROUGH, R. 1999. National prescribing centre: prescribing analysis terms.
<http://www.npc.co.uk/publications/prescribingTerms/bodybup.html> Date of access: 21 Jun. 2007.

RABENECK, L., SOUCHEK, J., WRISTERS, K., MENKE, T., AMBRIZ, E., HUANG, I. & WRAY, N. 2002. A double blind, randomized, placebo-controlled trial of proton pump inhibitor therapy in patients with uninvestigated dyspepsia. *American journal of gastroenterology*, 97:3045-3051.

RANG, H.P., DALE, M.M. & RITTER, J.M. 1999. Pharmacology. 4th ed. Edinburgh: Churchill Livingstone. 830 p.

REMAK, E., BROWN, R.E., YUEN, C. & ROBINSON, A. 2005. Cost-effectiveness comparison of current proton-pump inhibitors to treat gastro-oesophageal reflux disease in the UK. *Current medical research and opinion*, 21:1505-1517.

REPLOGLE, M.L., GLASER, S.L., HIATT, R.A. & PARSONNET, J. 1995. Biologic sex as a risk factor for *Helicobacter pylori* infection in healthy young adults. *American journal of epidemiology*, 142:856-863.

ROGNEHAUGH, R. 1998. The managed health care dictionary. 2nd ed. Gaithersburg: Aspen Publishers. 216p.

SACHS, G., SHIN, J.M., VAGIN, O., MUNSON, K., WEEKS, D., SCOTT, D.R. & VOLAND, P. 2002. Current trends in the treatment of upper gastrointestinal disease. *Best practice & research. Clinical gastroenterology*, 16:835-849.

SACRISTAN, J.A. & SOTO, J. 1994. Drug utilisation studies as tools in health economics. *Pharmaco-economics*, 5:299-312.

SALAS, M., WARD, A. & CARO, J. 2002. Are proton pump inhibitors the first choice for acute treatment of gastric ulcers? A meta-analysis of randomized clinical trials. *BMC gastroenterology*, 2:17. <http://www.biomedcentral.com/1471-230X/2/17> Date of access: 21 Apr. 2006.

SANCHEZ, L.A. 2005. Pharmaco-economics: principles, methods and applications. (In DiPiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G. & Posey, L.M., eds. *Pharmacotherapy: a pathophysiologic approach*. 6th ed. New York: McGraw-Hill. p. 1-15.)

SANDS, J.K. 1999. Management of persons with problems of the stomach and duodenum. (In Phipps, W.J., Sands, J.K. & Marek, J.F., eds. *Medical-surgical nursing: concepts & clinical practice*. 6th ed. St. Louis, Mo.: Mosby. p.1277-1312.)

SAS FOR WINDOWS 9.1. 2006. SAS Institute Inc., 2002-2003.

SERFONTEIN, J.H.P. 1989. Medisyneverbruik in provinsiale hospitale met besondere verwysing na die rol van die apteker in die beheerproses. Potchefstroom : PU vir CHO. (Thesis – D.Pharm.) 417p.

SERRADELL, J., BJORNSON, D.C. & HARTZEMA, A.G. 1987. Drug utilization study methodologies: national and international perspectives. *Drug intelligence and clinical pharmacy*, 21:994-1001.

SHIMAZU, T., MATSUI, T., FURUKAWA, K., OSHIGE, K., MITSUYASU, T., KITOMIZU, A., UEKI, T. & YAO, T. 2005. A prospective study of the prevalence of gastroesophageal reflux disease and confounding factors. *Journal of gastroenterology*, 40:866-872.

SNYMAN, J.R., ed. 2004. MIMS monthly index of medical specialities. *MIMS*, 44:1-367.

SNYMAN, J.R., ed. 2005. MIMS monthly index of medical specialities. *MIMS*, 45: 1-390.

SNYMAN, J.R., ed. 2007. MIMS monthly index of medical specialties. *MIMS*, 47: 1-491.

SOUTH AFRICA. 2003a. PSSA pharmacy law compendium. Durban: LexisNexisButterworths.

SOUTH AFRICA. Department of Health. 2003b. Government notice. *Government gazette*, 460(25537), Oct. 6.

SOUTH AFRICA. Department of Health. 2004. Government notice. *Government gazette*, 466(26304), Apr. 30.

SOUTH AFRICA. Department of Health. 2005. Government notice. *Government gazette*, 485(28214), Nov. 11.

SPADACCINI, A., DE FANIS, C., SCIAMPA, G., RUSSO, L., SILLA, M., PANTALEONE, U., DI VIRGILIO, M. & PIZZICANELLA, G. 1998. Triple regimens using lansoprazole or ranitidine bismuth citrate for *Helicobacter pylori* eradication. *Alimentary pharmacology & therapeutics*, 12:997-1001.

STALHAMMAR, N., CARLSSON, J., PEACOCK, R., MULLER-LISSNER, S., BIGARD, M., PORRO, G.B., PONCE, J., HOSIE, J., SCOTT, M., WEIR, D.G., FULTON, C., GILLON, K. & BARDHAN, K.D. 1999. Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-oesophageal reflux disease. *Pharmaco-economics*, 16:483-497.

STEYN, H.S. 1999. Praktiese beduidenheid: die effek van effekgroottes. Potchefstroom : PU vir CHO. 28p.

STRUWIG, V. 2001. Pharmaco-economics (FPHA 611). Potchefstroom: PU vir CHO. 167p. (Dictation)

SUNG, J.J.Y., CHAN, F.K.L., WU, J.C.Y., LEUNG, W.K., SUEN, R., LING, T.K.W., LEE, Y.T., CHENG, A.F.B. & SYDNEY CHUNG, S.C. 1999. One-week ranitidine bismuth citrate in combinations with metronidazole, amoxicillin and clarithromycin in the treatment of *Helicobacter pylori* infection: the RBC-MACH study. *Alimentary pharmacology & therapeutics*, 13:1079-1084.

SUNG, J.J.Y., LEUNG, W.K., LING, T.K.W., YUNG, M.Y., CHAN, F.K.L., LEE, Y.T., CHENG, A.F.B. & CHUNG, S.C.S. 1998. One-week use of ranitidine bismuth citrate, amoxicillin and clarithromycin for the treatment of *Helicobacter pylori*-related duodenal ulcer. *Alimentary pharmacology & therapeutics*, 12:725-730.

SUNOL, R., ABELLO, C. & CELS, I.C. 1991. Studies in utilization of drugs: a review of different methods. *Quality assurance in health care*, 3:63-72.

TALHEIMER, W. & COOK, S. 2002. How to calculate effect sizes from published research: a simplified methodology. <http://www.work-learning.com/Catalog/index.htm> Date of access: 22 May 2007.

TALLEY, N.J., ZINSMEISTER, A.R., SCHLECK, C.D. & MELTON, L.J. 1994. Smoking, alcohol, and analgesics in dyspepsia and among dyspepsia subgroups: lack of an association in a community. *Gut*, 35:619-624.

TALLEY, N.J., AXON, A., BYTZER, P., HOLTMANN, G., LAM, S.K. & VELOHUYZEN VAN ZANTEN, S. 1999a. Management of uninvestigated and functional dyspepsia: a working party

report for the World Congresses of Gastroenterology 1998. *Alimentary pharmacology & therapeutics*, 13:1135-1158.

TALLEY, N.J., STANGEHELLINI, V., HEADING, R.C., KOCH, K.L., MALAGELADA, J.R. & TYTGAT, G.N.J. 1999b. Functional gastroduodenal disorders. *Gut*, 45:37-42.
http://www.bmjjournals.com/cgi/content/full/45/suppl_2/I137 Date of access: 21 Apr. 2006.

THE FREE DICTIONARY. 2007. Percentage. <http://www.thefreedictionary.com/percentage>
Date of access: 10 Apr. 2007.

TREVOR, A.J., KATZUNG, B.G. & MASTERS, S.B. 2002. Katzung & Trevor's pharmacology: examination & broad review. 6th ed. New York: McGraw-Hill. 662p.

TRUTER, I. 1997. Opposite sides of the same coin: pharmaco-economics and drug utilisation. *SA pharmaceutical journal*, 64:19-20.

TRUTER, I. 2001. An overview of drug utilisation studies and rational drug therapy. Potchefstroom University for CHE: Potchefstroom. 45p.

TSHABALALA-MSIMANG, M. 2004. Finalisation of regulations on medicines pricing. *Pharmaciae*, 12:5-6.

TSHABALALA-MSIMANG, M. 2006. Announcement of the new dispensing fee for medicine. <http://www.doh.gov.za/docs/sp/2006/sp1031.html> Date of access: 26 Mar. 2007.

TUTUIAN, R. & CASTELL, D.O. 2003. Gastroesophageal reflux disease: natural history and long-term medical and surgical outcomes. *Clinical cornerstone*, 5:51-57.

U.S. PHARMACOPEIA DRUG UTILIZATION REVIEW ADVISORY PANEL. 2000. Drug utilization review: mechanisms to improve its effectiveness and broaden its scope. *Journal of the American Pharmaceutical Association*, 40:538-545.

UNITED STATES. FOOD AND DRUG ADMINISTRATION. Centre for Drug Evaluation and Research. 2007a. Consumer information. Generic drugs: questions and answers. http://www.fda.gov/cder/consumerinfo/generics_q&a.html Date of access: 6 May 2007.

UNITED STATES. FOOD AND DRUG ADMINISTRATION. Centre for Drug Evaluation and Research. 2007b. About the inactive ingredient database. <http://www.fda.gov/cder/iig/iigfaqWEB.htm#what%20is%20active%20ing> Date of access: 19 Sep. 2007.

VAKIL, N. 2004. New pharmacological agents for the treatment of gastro-oesophageal reflux disease. *Alimentary pharmacology & therapeutics*, 19:1041-1049.

VAKIL, N. & FENNERTY, M.B. 2003. Systematic review: direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Alimentary pharmacology & therapeutics*, 18:559-568.

VAN HOUT, B.A., KLOK, R.M., BROUWERS, J.R.B.J. & POSTMA, M.J. 2003. A pharmacoeconomic comparison of the efficacy and costs of pantoprazole for the treatment of peptic ulcer or gastroesophageal reflux disease in The Netherlands. *Clinical therapeutics*, 25:635-646.

VAN RENSBURG, C. (c.j.vr@telkomsa.net) 11 Apr. 2006. Request. E-mail to: Janse van Rensburg, D. (fpthnjvr@puknet.puk.ac.za).

VANDER, A.J., SHERMAN, J.H. & LUCIANO, D.S. 2001. Human physiology: the mechanisms of body function. 8th ed. Boston, Mass.: WCB/McGraw-Hill. 800 p.

VINCZE, A., KARADI, O., HUNYADY, B., PAKODI, F., SUTO, G. & MOZSIK, G. 2001. One year follow-up of patients after successful *Helicobacter pylori* eradication therapy. *Journal of physiology, Paris*, 95:457-460.

WAHLQVIST, P., JUNGHARD, O., HIGGINS, A. & GREEN, J. 2002a. Cost effectiveness of proton pump inhibitors in gastro-oesophageal reflux disease without oesophagitis: comparison of on-demand esomeprazole with conventional omeprazole strategies. *Pharmaco-economics*, 20:267-277.

WAHLQVIST, P., JUNGHARD, O., HIGGINS, A. & GREEN, J. 2002b. Cost effectiveness of esomeprazole compared with omeprazole in the acute treatment of patients with reflux oesophagitis in the UK. *Pharmaco-economics*, 20:279-287.

WALKOM, E., ROBERTSON, J., NEWBY, D. & PILLAY, T. 2006. The role of pharmacoeconomics in formulary decision-making: considerations for hospital and managed care pharmacy and therapeutics committees. *Formulary*, 41:374-386.

WALTERS, L. & SMART, A.J. 1993. Improving the cost-effective and rational utilisation of medicines in South Africa. *South African medical journal*, 84:820-821.

WANG, W.H., HUANG, J.Q., ZHENG, G.F., XIA, H.H.X., WONG, W.M., LAM, S.K. & WONG, B.C.Y. 2005. Head-to-head comparison of H₂-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. *World journal of gastroenterology*, 11:4067-4077.

WERTHEIMER, A.I. 1988. Quality control and drug utilization review. *Pharmaceutisch weekblad. Scientific edition*, 10:154-157.

WESTBROOK, J.I., MCINTOSH, J. & TALLEY, N.J. 2000. Factors associated with consulting medical or non-medical practitioners for dyspepsia: an Australian population-based study. *Alimentary pharmacology & therapeutics*, 14:1581-1588.

WHITAKER, M.J. 1998. Consensus guidelines for evaluating and treating patients with upper gastrointestinal symptoms in the primary care setting. *Pharmaco-economics*, 14(Suppl.2):5-10.

WHO see **WORLD HEALTH ORGANIZATION.**

WORLD HEALTH ORGANIZATION. 2003. Introduction to drug utilization research. http://www.who.int/entity/medicines/areas/quality_safety/safety_efficacy/Drug%20utilization%research.pdf Date of access: 20 Jun. 2007.

WORLD HEALTH ORGANIZATION. Collaborating Centre for Drug Statistics Methodology. 2007a. History of the ATC/DDD system. <http://www.whocc.no/atsddd> Date of access: 27 Sep. 2007.

WORLD HEALTH ORGANIZATION. Collaborating Centre for Drug Statistics Methodology. 2007b. ATC/DDD index. <http://www.whocc.no/atsddd> Date of access: 28 Sep. 2007.

YOGENDRAN, M. & METGE, C. 2004. Dose intensity. http://www.umanitoba.ca/centres/mchp/concept/dict/drug/dose_intensity.html Date of access: 21 Jun. 2007.

ZAGARI, M., VILLA, K.F. & FRESTON, J.W. 1995. Proton pump inhibitors versus H₂-receptor antagonists for the treatment of erosive gastroesophageal reflux disease: a cost-comparative study. *American journal of managed care*, 1:247-255.

Table A1: The prevalence percentage of acid reducing medicine items according to active ingredient for years 2001, 2002, 2004, 2005 and 2006.

Year	2001		2002		2004		2005		2006	
Active ingredient	Prevalence	%	Prevalence	%	Prevalence	%	Prevalence	%	Prevalence	%
Antacids	24 674	30.54	32 560	30.24	38 409	28.37	25 066	27.08	15 879	26.84
H₂RA										
Cimetidine	4 646	5.75	5 317	4.17	5 292	3.91	2 505	2.71	1 053	1.78
Famotidine	84	0.10	71	0.07	107	0.08	0	0.00	0	0.00
Nizatidine	45	0.06	183	0.17	233	0.17	174	0.19	95	0.16
Ranitidine	7 831	9.70	10 543	9.83	15 229	11.25	12 578	13.59	9 652	16.34
Ranitidine bismuth citrate	0	0.00	33	0.03	0	0.00	0	0.00	0	0.00
PPIs										
Esomeprazole	0	0.00	5 984	5.56	19 332	14.28	10532	11.38	4 274	7.22
Lansoprazole	14 855	18.39	16 965	15.76	17 383	12.84	9163	9.90	5 413	9.15
Omeprazole	12 689	15.71	16 325	15.17	13 291	9.82	15 627	16.88	13 808	23.34
Omeprazole/Amoxicillin/ clarithromycin	266	0.33	278	0.26	46	0.03	2	0.00	0	0.00
Pantoprazole	5 986	7.41	7 552	7.02	14 266	10.54	82 55	8.92	3 817	6.45
Rabeprazole	5 934	7.35	7 265	6.75	6 961	5.14	50 79	5.49	3 205	5.41
Cytoprotective agents										
Bismuth	147	0.18	69	0.06	99	0.07	52	0.06	20	0.03
Misoprostol	360	0.45	426	0.40	498	0.37	2 96	0.32	225	0.38
Sucralfate	3 256	4.03	4 066	3.78	4 255	3.14	32 36	3.50	1 716	2.90
TOTAL	80 773	100.00	107 637	99.27	135 401	100.01	925 65	100.02	59 157	100.00

% - The total number of medicine items per active ingredient claimed for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred.

Table B1: The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RAs										
Cimetidine	Tagamet S [®] 200mg	Syr	Innovator	1	346.77	0.00	346.77	0.00	0.00	1.51
			SUBTOTAL	1	346.77	0.00	346.77	0.00	0.00	1.51
	Tagamet [®] 200mg	Amp	Innovator	2	31.03	3.77	62.05	0.00	0.00	0.13
			SUBTOTAL	2	31.03	3.77	62.05	0.00	0.00	0.13
	Tagamet [®] 200mg	Tab	Innovator	29	352.19	367.44	10 213.61	0.04	0.05	1.53
	Acidown [®] 200mg	Tab	Generic	18	127.03	96.17	2 286.60	0.02	0.01	0.55
	Aci-med [®] 200mg	Tab	Generic	18	106.58	57.35	1 918.46	0.02	0.01	0.46
	Aci-med OTC [®]	Tab	Generic	51	38.75	13.98	1 976.27	0.06	0.01	0.17
	Adco-cimetidine [®] 200mg	Tab	Generic	225	95.83	53.99	21 562.09	0.28	0.12	0.42
	Apo-cimetidine [®] 200mg	Tab	Generic	3	66.42	15.96	199.25	0.00	0.00	0.29
	Cimlok [®] 200mg	Tab	Generic	53	76.36	47.57	4 047.11	0.07	0.02	0.33
	Cinadine [®] 200mg	Tab	Generic	4	91.45	54.96	365.78	0.00	0.00	0.40
	Cymi [®] 200mg	Tab	Generic	1	25.31	0.00	25.31	0.00	0.00	0.11
	Hexamet [®] 200mg	Tab	Generic	96	71.01	28.03	6 816.78	0.12	0.04	0.31
	Lenamet [®] 200mg	Tab	Generic	489	83.70	42.54	40 928.18	0.61	0.22	0.36
	Lenamet OTC [®]	Tab	Generic	220	44.74	24.59	9 843.01	0.27	0.05	0.19
	Secadine [®] 200mg	Tab	Generic	6	101.03	60.26	606.16	0.01	0.00	0.44
	Rolab-cimetidine [®] 200mg	Tab	Generic	3	56.78	95.46	170.35	0.00	0.00	0.25
	Ulcim [®] 200mg	Tab	Generic	6	64.76	42.32	388.54	0.01	0.00	0.28
			SUBTOTAL	1 222	82.94	83.69	101 347.50	1.51	0.55	0.36

Table B1 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RAs										
Cimetidine	Tagamet® 400mg	Tab	Innovator	39	274.52	128.94	10 706.15	0.05	0.06	1.19
	Aci-med® 400mg	Tab	Generic	72	219.45	86.82	15 800.30	0.09	0.09	0.95
	Adco-cimetidine® 400mg	Tab	Generic	978	194.66	87.24	190 379.50	1.21	1.02	0.85
	Apo-cimetidine® 400mg	Tab	Generic	9	213.48	106.23	1 921.38	0.01	0.01	0.93
	Cimlok® 400mg	Tab	Generic	264	172.14	82.23	45 444.12	0.33	0.24	0.75
	Cinadine® 400mg	Tab	Generic	163	176.69	83.94	28 799.91	0.20	0.15	0.77
	Duomet® 400mg	Tab	Generic	3	237.89	71.93	713.68	0.00	0.00	1.03
	Hexamet® 400mg	Tab	Generic	602	179.60	88.01	108 116.84	0.75	0.58	0.78
	Lenamet® 400mg	Tab	Generic	1 191	175.32	83.33	208 802.35	1.47	1.12	0.76
	Secadine® 400mg	Tab	Generic	70	203.07	80.29	14 215.16	0.09	0.08	0.88
	Rolab-cimetidine® 400mg	Tab	Generic	21	172.25	71.90	3 617.20	0.03	0.02	0.75
	Ulcim® 400mg	Tab	Generic	9	195.65	92.13	1 760.84	0.01	0.01	0.85
			SUBTOTAL	3 421	184.24	86.98	630 277.43	4.24	3.39	0.80
			TOTAL	4 646			732 033.75	5.75	3.94	0.69
Famotidine	Pepsid® 20mg	Tab	Innovator	40	255.89	101.74	10 235.59	0.05	0.06	1.11
			SUBTOTAL	40	255.89	101.74	10 235.59	0.05	0.06	1.11
	Pepsid® 40mg	Tab	Innovator	44	601.91	191.01	26 484.20	0.05	0.14	2.62
			SUBTOTAL	44	601.91	191.01	26 484.20	0.05	0.14	2.62
			TOTAL	84			36 719.79	0.10	0.20	1.90

Table B1 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RAs										
Nizatidine	Antizid® 150 mg	Cap	Innovator	45	243.82	209.52	10 971.91	0.06	0.06	1.06
			TOTAL	45	243.82	209.52	10 971.91	0.06	0.06	1.06
Ranitidine	Zantac®	Syr	Innovator	42	172.28	99.74	7 235.81	0.05	0.04	0.75
			SUBTOTAL	42	172.28	99.74	7 235.81	0.05	0.04	0.75
	Zantac® 2ml/50mg	Inj	Innovator	6	270.48	190.52	1 622.89	0.01	0.01	1.18
			SUBTOTAL	6	270.48	190.52	1 622.89	0.01	0.01	1.18
	Zantac® 75mg	Tab	Innovator	908	83.76	43.02	76 055.94	1.12	0.41	0.36
	Histak® 75 mg	Tab	Generic	29	93.97	63.77	2 725.23	0.04	0.01	0.41
	Ulcaid® 75mg	Tab	Generic	90	60.78	46.46	5 470.31	0.11	0.03	0.26
			SUBTOTAL	1 027	82.04	44.50	84 251.48	1.27	0.45	0.36
	Zantac® 150mg	Tab	Innovator	523	240.07	112.59	125 561.22	0.65	0.68	1.04
	Apo-ranitidine® 150mg	Tab	Generic	202	242.46	82.82	48 976.69	0.25	0.26	1.05
	Garec-ranitidine® 150mg	Tab	Generic	185	193.72	85.17	35 837.66	0.23	0.19	0.84
	Histak® 150mg	Tab	Generic	494	226.78	91.06	112 031.23	0.61	0.60	0.99
	Ranihexal® 150mg	Tab	Generic	1 208	162.24	92.11	195 984.17	1.50	1.05	0.71
	Ranteen® 150mg	Tab	Generic	73	193.36	91.72	14 114.95	0.09	0.08	0.84
	Ulcaid® 150mg	Tab	Generic	189	201.00	104.62	37 988.69	0.23	0.20	0.87
	Ultak® 150mg	Tab	Generic	809	113.17	62.52	91 555.24	1.00	0.49	0.49
			SUBTOTAL	3 683	179.76	100.73	662 049.85	4.56	3.56	0.78

Table B1 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RAs										
Ranitidine	Zantac® 300mg	Tab	Innovator	187	312.78	119.47	58 489.70	0.23	0.31	1.36
	Apo-ranitidine® 300mg	Tab	Generic	38	280.33	72.83	10 652.63	0.05	0.06	1.22
	Garec-ranitidine® 300mg	Tab	Generic	91	209.61	80.71	19 074.64	0.11	0.10	0.91
	Histak® 300mg	Tab	Generic	216	254.61	86.62	54 995.15	0.27	0.30	1.11
	Ranihexal® 300mg	Tab	Generic	542	233.31	84.59	126 455.41	0.67	0.68	1.01
	Ranteen® 300mg	Tab	Generic	21	208.07	141.67	4 369.42	0.03	0.02	0.90
	Ulcaid® 300mg	Tab	Generic	50	241.99	73.50	12 099.34	0.06	0.07	1.05
	Ultak® 300mg	Tab	Generic	221	147.93	86.69	32 692.67	0.27	0.18	0.64
			SUBTOTAL	1 366	233.40	102.29	318 828.96	1.69	1.72	1.01
	Zantac® eff 150mg	Tab	Innovator	1 501	159.01	84.20	238 666.59	1.86	1.28	0.69
			SUBTOTAL	1 501	159.01	84.20	238 666.59	1.86	1.28	0.69
	Zantac® eff 300mg	Tab	Innovator	206	427.16	135.16	87 994.10	0.26	0.47	1.86
			SUBTOTAL	206	427.16	135.16	87 994.10	0.26	0.47	1.86
			TOTAL	7 831			1 400 649.68	9.70	7.54	0.78
PPIs										
Omeprazole /amoxicillin/ clarithromycin	Losec 20 Triple pack®	Cap	Innovator	266	678.84	121.38	180 572.15	0.33	0.97	2.95
			TOTAL	266	678.84	121.38	180 572.15	0.33	0.97	2.95

Table B1 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Lansoprazole	Lanzor [®] 15mg	Cap	Innovator	5 151	287.33	78.86	1 480 051.48	6.38	7.97	1.25
			SUBTOTAL	5 151	287.33	78.86	1 480 051.48	6.38	7.97	1.25
	Lanzor [®] 30 mg	Cap	Innovator	9 704	398.42	151.63	3 866 295.47	12.01	20.81	1.73
			SUBTOTAL	9 704	398.42	151.63	3 866 295.47	12.01	20.81	1.73
			TOTAL	14 855			5 346 346.95	18.39	28.77	1.56
Omeprazole	Losec mups [®] 10mg	Tab	Innovator	3 354	286.17	77.92	959 827.11	4.15	5.17	1.24
	Ulzec [®] 10mg	Cap	Generic	153	210.72	82.76	32 240.29	0.19	0.17	0.92
			SUBTOTAL	3 507	282.88	79.63	992 067.40	4.34	5.34	1.23
	Losec mups [®] 20mg	Tab	Innovator	8 361	413.35	152.36	3 456 060.37	10.35	18.60	1.80
	Ulzec [®] 20mg	Cap	Generic	518	305.14	161.27	158 061.25	0.64	0.85	1.33
			SUBTOTAL	8 879	407.04	154.98	3 614 121.62	10.99	19.45	1.77
	Losec mups [®] 40mg	Tab	Innovator	303	630.56	283.43	191 060.01	0.38	1.03	2.74
			SUBTOTAL	303	630.56	283.43	191 060.01	0.38	1.03	2.74
			TOTAL	12 689			4 797 249.03	15.71	25.82	1.64

Table B1 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2001.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std Dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Pantoprazole	Pantoloc® IV 40mg	Inj	Innovator	1	279.69	0.00	279.69	0.00	0.00	1.22
			SUBTOTAL	1	279.69	0.00	279.69	0.00	0.00	1.22
	Controloc® 20mg	Tab	Innovator	50	248.10	63.68	12 404.91	0.06	0.07	1.08
	Pantoloc® 20mg	Tab	Innovator	418	249.59	85.24	104 308.25	0.52	0.56	1.08
			SUBTOTAL	468	249.39	83.15	116 713.16	0.58	0.63	1.08
	Controloc® 40mg	Tab	Innovator	2 133	371.90	125.21	793 267.95	2.64	4.27	1.62
	Pantoloc® 40mg	Tab	Innovator	3 384	391.47	141.87	1 324 728.59	4.19	7.13	1.70
			SUBTOTAL	5 517	383.90	135.99	2 117 996.54	6.83	11.40	1.67
			TOTAL	5 986			2 234 989.39	7.41	12.03	1.62
Rabeprazole	Pariet® 10mg	Tab	Innovator	2 231	233.52	64.28	520 978.63	2.76	2.80	1.02
			SUBTOTAL	2 231	233.52	64.28	520 978.63	2.76	2.80	1.02
	Pariet® 20mg	Tab	Innovator	3 703	318.70	133.45	1 180 139.47	4.58	6.35	1.39
			SUBTOTAL	3 703	318.70	133.45	1 180 139.47	4.58	6.35	1.39
			TOTAL	5 934			1 701 118.10	7.35	9.16	1.25

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of acid reducers for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table B2: The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Tagamet® 200mg	Tab	Innovator	9	90.52	63.18	814.67	0.01	0.00	0.37
	Acidown® 200mg	Tab	Generic	2	42.88	16.10	85.76	0.00	0.00	0.18
	Aci-med OTC®	Tab	Generic	38	46.80	16.61	1 778.53	0.04	0.01	0.19
	Adco-cimetidine® 200mg	Tab	Generic	275	79.08	41.42	21 747.61	0.26	0.08	0.32
	Cimlok® 200mg	Tab	Generic	68	76.71	36.81	5 215.94	0.06	0.02	0.31
	Hexamet® 200mg	Tab	Generic	112	66.70	32.34	7 470.10	0.10	0.03	0.27
	Lenamet® 200mg	Tab	Generic	502	73.78	38.77	37 036.64	0.47	0.14	0.30
	Lenamet OTC®	Tab	Generic	450	46.45	24.12	20 903.53	0.42	0.08	0.19
	Secadine® 200mg	Tab	Generic	16	64.83	33.20	1 037.35	0.01	0.00	0.27
	Rolab-cimetidine® 200mg	Tab	Generic	15	66.10	31.80	991.45	0.01	0.00	0.27
			SUBTOTAL	1 487	65.29	37.07	97 081.58	1.38	0.37	0.27

Table B2 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Tagamet® 400mg	Tab	Innovator	27	264.24	117.92	7 134.45	0.03	0.03	1.08
	Aci-med® 400mg	Tab	Generic	68	204.46	98.32	13 902.98	0.06	0.05	0.84
	Adco-cimetidine® 400mg	Tab	Generic	896	188.68	85.75	169 053.69	0.83	0.64	0.77
	Cimlok® 400mg	Tab	Generic	344	175.37	79.35	60 326.04	0.32	0.23	0.72
	Cinadine® 400mg	Tab	Generic	104	163.01	65.26	16 952.72	0.10	0.06	0.67
	Duomet® 400mg	Tab	Generic	2	279.43	0.00	558.86	0.00	0.00	1.15
	Hexamet® 400mg	Tab	Generic	691	185.30	87.71	128 044.82	0.64	0.49	0.76
	Lenamet® 400mg	Tab	Generic	1 448	172.41	98.04	249 644.91	1.35	0.95	0.71
	Secadine® 400mg	Tab	Generic	152	180.62	101.89	27 454.81	0.14	0.10	0.74
	Rolab-cimetidine® 400mg	Tab	Generic	94	200.27	83.52	18 825.58	0.09	0.07	0.82
	Ulcim® 400mg	Tab	Generic	4	259.21	110.07	1 036.83	0.00	0.00	1.06
			SUBTOTAL	3 830	180.92	91.67	692 935.69	3.56	2.64	0.74
			TOTAL	5 317			790 017.27	4.94	3.01	0.61
Famotidine	Pepsid® 20mg	Tab	Innovator	4	117.79	49.98	471.15	0.00	0.00	0.48
			SUBTOTAL	4	117.79	49.98	471.15	0.00	0.00	0.48
	Pepsid® 40mg	Tab	Innovator	67	460.60	369.22	30 859.96	0.06	0.12	1.89
			SUBTOTAL	67	460.60	369.22	30 859.96	0.06	0.12	1.89
			TOTAL	71			31 331.11	0.07	0.12	1.81
Nizatidine	Antizid® 150 mg	Cap	Innovator	183	248.18	149.56	45 416.38	0.17	0.17	1.02
			TOTAL	183	248.18	149.56	45 416.38	0.17	0.17	1.02

Table B2 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac®	Syr	Innovator	37	225.23	134.91	8 333.33	0.03	0.03	0.92
			SUBTOTAL	37	225.23	134.91	8 333.33	0.03	0.03	0.92
	Zantac® 2ml/50mg	Inj	Innovator	6	219.99	221.48	1 319.91	0.01	0.01	0.90
			SUBTOTAL	6	219.99	221.48	1 319.91	0.01	0.01	0.90
	Zantac® 75mg	Tab	Innovator	1 006	80.17	44.43	80 646.53	0.93	0.31	0.33
	Histak® 75 mg	Tab	Generic	255	64.65	39.73	16 486.64	0.24	0.06	0.27
	Ulcaid® 75mg	Tab	Generic	172	61.02	44.66	10 494.77	0.16	0.04	0.25
			SUBTOTAL	1 433	75.11	44.32	107 627.94	1.33	0.41	0.31
	Zantac® 150mg	Tab	Innovator	538	249.45	131.85	134 206.54	0.50	0.51	1.02
	Apo-ranitidine® 150mg	Tab	Generic	66	240.04	85.22	15 842.75	0.06	0.06	0.98
	CPL ranitidine® 150mg		Generic	3	238.31	109.41	714.94	0.00	0.00	0.98
	Garec-ranitidine® 150mg	Tab	Generic	31	233.28	88.01	7 231.77	0.03	0.03	0.96
	Histak® 150mg	Tab	Generic	971	207.75	91.58	201 727.07	0.90	0.77	0.85
	Ranihexal® 150mg	Tab	Generic	1 881	158.71	88.44	298 529.15	1.75	1.14	0.65
	Ranteen® 150mg	Tab	Generic	40	220.76	86.47	8 830.38	0.04	0.03	0.91
	Ulcaid® 150mg	Tab	Generic	72	236.90	108.34	17 056.94	0.07	0.07	0.97
	Ultak® 150mg	Tab	Generic	1 459	120.59	62.83	17 5934.79	1.36	0.67	0.49
			SUBTOTAL	5 061	169.94	98.66	86 0074.33	4.70	3.28	0.70

Table B2 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac [®] 300mg	Tab	Innovator	260	365.78	199.59	95 103.76	0.24	0.36	1.50
	Apo-ranitidine [®] 300mg	Tab	Generic	14	177.49	56.90	2 484.39	0.01	0.01	0.73
	Garec-ranitidine [®] 300mg	Tab	Generic	41	202.91	65.65	8 319.28	0.04	0.03	0.83
	Histak [®] 300mg	Tab	Generic	296	174.07	73.05	51 524.28	0.27	0.20	0.71
	Ranihexal [®] 300mg	Tab	Generic	534	171.08	65.53	91 354.95	0.50	0.35	0.70
	Ranteen [®] 300mg	Tab	Generic	42	185.12	64.69	7 775.23	0.04	0.03	0.76
	Ulcaid [®] 300mg	Tab	Generic	16	266.32	76.73	4 261.19	0.01	0.02	1.09
	Ultak [®] 300mg	Tab	Generic	587	175.79	72.10	103 186.42	0.55	0.39	0.72
			SUBTOTAL	1 790	203.36	120.33	364 010.00	1.66	1.39	0.83
	Zantac [®] eff 150mg	Tab	Innovator	1 838	199.26	110.60	366 239.26	1.71	1.40	0.82
			SUBTOTAL	1 838	199.26	110.60	366 239.26	1.71	1.40	0.82
	Zantac [®] eff 300mg	Tab	Innovator	378	428.95	151.01	162 142.35	0.35	0.62	1.76
			SUBTOTAL	378	428.95	151.01	162 142.35	0.35	0.62	1.76
			TOTAL	10 543			1 869 746.62	9.79	7.13	0.73
Ranitidine bismuth citrate	Pylorid [®] 400mg	Tab	Innovator	33	288.23	82.04	9 511.46	0.03	0.04	1.18
			TOTAL	33	288.23	82.04	9 511.46	0.03	0.04	1.18

Table B2 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Omeprazole /amoxicillin/ clarithromycin	Losec 20 Triple pack [®]		Innovator	278	740.31	99.83	205 806.22	0.26	0.78	3.04
			TOTAL	278	740.31	99.83	205 806.22	0.26	0.78	3.04
Lansoprazole	Lanzor [®] 15mg	Cap	Innovator	6 322	327.87	74.55	2 072 788.25	5.87	7.90	1.35
			SUBTOTAL	6 322	327.87	74.55	2 072 788.25	5.87	7.90	1.35
	Lanzor [®] 30 mg	Cap	Innovator	10 643	445.06	161.52	4 736 747.05	9.89	18.06	1.83
			SUBTOTAL	10 643	445.06	161.52	4 736 747.05	9.89	18.06	1.83
			TOTAL	16 965			6 809 535.30	15.76	25.96	1.65
Esomeprazole	Nexiam [®] 20mg	Tab	Innovator	1 924	279.97	98.81	538 666.27	1.79	2.05	1.15
			SUBTOTAL	1 924	279.97	98.81	538 666.27	1.79	2.05	1.15
	Nexiam [®] 40mg	Tab	Innovator	4 060	368.23	160.21	1 494 997.59	3.77	5.70	1.51
			SUBTOTAL	4 060	368.23	160.21	1 494 997.59	3.77	5.70	1.51
			TOTAL	5 984			2 033 663.86	5.56	7.75	1.39
Omeprazole	Losec mups [®] 10mg	Tab	Innovator	3 336	302.90	89.25	1 010 473.75	3.10	3.85	1.24
	Ulzec [®] 10mg	Cap	Generic	1 380	218.01	74.59	300 858.80	1.28	1.15	0.89
			SUBTOTAL	4 716	278.06	93.56	1 311 332.55	4.38	5.00	1.14
	Losec mups [®] 20mg	Tab	Innovator	7 452	437.64	170.57	3 261 315.59	6.92	12.43	1.80
	Ulzec [®] 20mg	Cap	Generic	3 971	308.67	125.90	1 225 733.21	3.69	4.67	1.27
			SUBTOTAL	11 423	392.81	168.11	4 487 048.80	10.61	17.10	1.61
	Losec mups [®] 40mg	Tab	Innovator	186	738.17	409.75	137 299.35	0.17	0.52	3.03
			SUBTOTAL	186	738.17	409.75	137 299.35	0.17	0.52	3.03
			TOTAL	16 325			5 935 680.70	15.17	22.63	1.49

Table B2 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2002.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Pantoprazole	Pantoloc® IV 40mg	Inj	Innovator	1	330.84	0.00	330.84	0.00	0.00	1.36
			SUBTOTAL	1	330.84	0.00	330.84	0.00	0.00	1.36
	Controloc® 20mg	Tab	Innovator	717	249.93	82.90	179 203.19	0.67	0.68	1.03
	Pantoloc® 20mg	Tab	Innovator	1 297	253.95	62.02	329 373.03	1.20	1.26	1.04
			SUBTOTAL	2 014	252.52	70.18	508 576.22	1.87	1.94	1.04
	Controloc® 40mg	Tab	Innovator	2 510	393.67	141.71	988 109.56	2.33	3.77	1.62
	Pantoloc® 40mg	Tab	Innovator	3 027	416.33	138.81	1 260 234.52	2.81	4.80	1.71
			SUBTOTAL	5 537	406.58	140.57	2 248 344.08	5.14	8.57	1.67
			TOTAL	7 552			2 757 251.14	7.02	10.51	1.50
Rabeprazole	Pariet® 10mg	Tab	Innovator	2 864	288.25	72.54	825 553.31	2.66	3.15	1.18
			SUBTOTAL	2 864	288.25	72.54	825 553.31	2.66	3.15	1.18
	Pariet® 20mg	Tab	Innovator	4 401	381.87	161.92	1 680 621.53	4.09	6.41	1.57
			SUBTOTAL	4 401	381.87	161.92	1 680 621.53	4.09	6.41	1.57
			TOTAL	7 256			2 506 174.84	6.74	9.55	1.42

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of acid reducers for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table B3: The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Sabax cimetidine® 200mg	Amp	Generic	8	57.86	53.71	462.89	0.01	0.00	0.28
			SUBTOTAL	8	57.86	53.71	462.89	0.01	0.00	0.28
	Tagamet® 200mg	Tab	Innovator	11	115.55	95.27	1 270.95	0.01	0.00	0.56
	Acidown® 200mg	Tab	Generic	2	7.10	3.35	14.20	0.00	0.00	0.03
	Adco-cimetidine® 200mg	Tab	Generic	260	37.43	22.61	9 731.87	0.19	0.03	0.18
	Bio-cimetidine® 200mg	Tab	Generic	18	30.55	46.74	549.91	0.01	0.00	0.15
	Cimlok® 200mg	Tab	Generic	209	33.02	33.01	6 900.36	0.15	0.02	0.16
	Hexamet® 200mg	Tab	Generic	107	36.39	26.66	3 894.08	0.08	0.01	0.18
	Lenamet® 200mg	Tab	Generic	461	33.91	28.88	15 634.50	0.34	0.06	0.16
	Lenamet OTC®	Tab	Generic	339	31.99	18.08	10 843.11	0.25	0.04	0.16
	Secadine® 200mg	Tab	Generic	11	30.98	15.60	340.83	0.01	0.00	0.15
	Rolab-cimetidine® 200mg	Tab	Generic	33	51.29	30.57	1 692.69	0.02	0.01	0.25
			SUBTOTAL	1 451	35.06	28.49	50 872.50	1.07	0.18	0.17

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Tagamet® 400mg	Tab	Innovator	24	221.55	231.98	5 317.15	0.02	0.02	1.07
	Aci-med® 400mg	Tab	Generic	10	83.67	103.82	836.66	0.01	0.00	0.41
	Adco-cimetidine® 400mg	Tab	Generic	926	85.06	87.30	78 766.18	0.68	0.28	0.41
	Bio-cimetidine® 400mg	Tab	Generic	45	57.35	64.64	2 580.57	0.03	0.01	0.28
	Cimlok® 400mg	Tab	Generic	515	77.04	85.00	39 674.58	0.38	0.14	0.37
	Cinadine® 400mg	Tab	Generic	50	130.88	93.33	6 544.04	0.04	0.02	0.63
	Hexamet® 400mg	Tab	Generic	449	80.51	77.65	36 147.28	0.33	0.13	0.39
	Lenamet® 400mg	Tab	Generic	1 569	75.42	78.14	118 329.90	1.16	0.42	0.37
	Secadine® 400mg	Tab	Generic	68	75.48	77.96	5 132.59	0.05	0.02	0.37
	Rolab-cimetidine® 400mg	Tab	Generic	177	102.30	105.19	18 106.49	0.13	0.06	0.50
			SUBTOTAL	3 833	81.25	85.66	311 435.44	2.83	1.12	0.39
			TOTAL	5 292			362 770.83	3.91	1.30	0.33
Famotidine	Pepsid® 40mg	Tab	Innovator	107	484.60	100.72	51 851.67	0.08	0.19	2.35
			TOTAL	107			51 851.67	0.08	0.19	2.35
Nizatidine	Antizid® 150 mg	Cap	Innovator	233	221.78	134.62	51 674.85	0.17	0.19	1.08
			TOTAL	233	221.78	134.62	51 674.85	0.17	0.19	1.08

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac®	Syr	Innovator	76	166.85	132.61	12 680.65	0.06	0.05	0.81
			SUBTOTAL	76	166.85	132.61	12 680.65	0.06	0.05	0.81
	Zantac® 2ml/50mg	Inj	Innovator	99	125.46	205.40	12 420.69	0.07	0.04	0.61
			SUBTOTAL	99	125.46	205.40	12 420.69	0.07	0.04	0.61
	Zantac® 75mg	Tab	Innovator	327	62.85	38.82	20 551.34	0.24	0.07	0.30
	Gi-tak® 75mg	Tab	Generic	24	50.83	85.57	1 220.00	0.02	0.00	0.25
	Histak® 75 mg	Tab	Generic	395	39.58	23.53	15 635.09	0.29	0.06	0.19
	Ulcaid® 75mg	Tab	Generic	6	29.92	10.98	179.52	0.00	0.00	0.15
	Ultak® 75mg	Tab	Generic	2	25.61	0.00	51.22	0.00	0.00	0.12
			SUBTOTAL	754	49.92	36.05	37 637.17	0.56	0.13	0.24
	Zantac® 150mg	Tab	Innovator	445	319.39	196.03	142 127.15	0.33	0.51	1.55
	Apo-ranitidine® 150mg	Tab	Generic	13	77.99	56.62	1 013.90	0.01	0.00	0.38
	Be-tabs ranitidine® 150mg	Tab	Generic	29	39.08	23.30	1 133.45	0.02	0.00	0.19
	CPL ranitidine® 150mg	Tab	Generic	32	69.08	73.96	2 210.44	0.02	0.01	0.34
	Histak® 150mg	Tab	Generic	2 586	70.55	59.89	182 445.01	1.91	0.65	0.34
	Ranihexal® 150mg	Tab	Generic	2 297	89.74	68.96	206 136.75	1.70	0.74	0.44
	Ranteen® 150mg	Tab	Generic	26	135.81	89.06	3 531.06	0.02	0.01	0.66
	Ulcaid® 150mg	Tab	Generic	6	168.91	139.34	1 013.44	0.00	0.00	0.82
	Ultak® 150mg	Tab	Generic	2 211	71.26	56.73	157 546.99	1.63	0.56	0.35
			SUBTOTAL	7 645	91.19	95.85	697 158.19	5.65	2.50	0.44

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac® 300mg	Tab	Innovator	282	506.11	221.98	142 722.54	0.21	0.51	2.45
	Apo-ranitidine® 300mg	Tab	Generic	1	1.32	0.00	1.32	0.00	0.00	0.01
	Be-tabs ranitidine® 300mg	Tab	Generic	29	51.37	41.34	1 489.86	0.02	0.01	0.25
	CPL ranitidine® 300mg	Tab	Generic	36	100.32	68.78	3 611.57	0.03	0.01	0.49
	Histak® 300mg	Tab	Generic	714	106.67	78.67	76 165.51	0.53	0.27	0.52
	Ranixhexal® 300mg	Tab	Generic	1 077	94.58	67.10	101 866.79	0.80	0.36	0.46
	Ranteen® 300mg	Tab	Generic	7	187.11	110.59	1 309.78	0.01	0.00	0.91
	Ulcaid® 300mg	Tab	Generic	9	292.34	96.93	2 631.08	0.01	0.01	1.42
	Ultak® 300mg	Tab	Generic	1 023	117.95	84.08	120 667.13	0.76	0.43	0.57
			SUBTOTAL	3 178	141.74	151.08	450 465.58	2.35	1.61	0.69
	Zantac® eff 75mg	Tab	Innovator	163	62.78	50.40	10 233.36	0.12	0.04	0.30
			SUBTOTAL	163	62.78	50.40	10 233.36	0.12	0.04	0.30
	Zantac® eff 150mg	Tab	Innovator	2 662	260.12	156.84	692 443.26	1.97	2.48	1.26
			SUBTOTAL	2 662	260.12	156.84	692 443.26	1.97	2.48	1.26
	Zantac® eff 300mg	Tab	Innovator	652	497.65	217.61	324 468.17	0.48	1.16	2.41
			SUBTOTAL	652	497.65	217.61	324 468.17	0.48	1.16	2.41
			TOTAL	15 229			2 237 507.07	11.25	8.01	0.71

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Omeprazole /amoxicillin/ clarithromycin	Losec 20 Triple pack®	Cap	Innovator	46	676.80	194.10	31 132.77	0.03	0.11	3.28
			TOTAL	46	676.80	194.10	31 132.77	0.03	0.11	3.28
Lansoprazole	Lanzor® 15mg	Cap	Innovator	6 742	280.25	94.88	1 889 423.35	4.98	6.77	1.36
	Lanzor® HB	Cap	Innovator	67	131.84	84.72	8 833.42	0.05	0.03	0.64
			SUBTOTAL	6 809	278.79	95.91	1 898 256.77	5.03	6.80	1.35
	Lanzor® 30 mg	Cap	Innovator	10 574	386.94	164.00	4 091 488.46	7.81	14.66	1.88
			SUBTOTAL	10 574	386.94	164.00	4 091 488.46	7.81	14.66	1.88
			TOTAL	17 383			5 989 745.23	12.84	21.45	1.67
Esomeprazole	Nexiam® 20mg	Tab	Innovator	8 972	240.23	89.23	2 155 314.28	6.63	7.72	1.17
			SUBTOTAL	8 972	240.23	89.23	2 155 314.28	6.63	7.72	1.17
	Nexiam® 40mg	Tab	Innovator	10 360	331.16	156.55	3 430 848.83	7.65	12.29	1.61
			SUBTOTAL	10 360	331.16	156.55	3 430 848.83	7.65	12.29	1.61
			TOTAL	19 332			5 586 163.11	14.28	20.01	1.40

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Omeprazole	Losec mups® 10mg	Tab	Innovator	2 746	267.43	102.54	734 372.36	2.03	2.63	1.30
	Omez® 10mg	Cap	Generic	106	116.60	62.33	12 359.68	0.08	0.04	0.57
	Ulzec® 10mg	Cap	Generic	6	200.90	90.60	1 205.40	0.00	0.00	0.97
			SUBTOTAL	2 858	261.70	105.26	747 937.44	2.11	2.68	1.27
	Losec mups® 20mg	Tab	Innovator	6 437	419.07	193.92	2 697 546.33	4.75	9.66	2.03
	Adco-omeprazole® 20 mg	Cap	Generic	1 535	92.76	80.54	142 390.01	1.13	0.51	0.45
	Omez® 20mg	Cap	Generic	712	123.99	63.61	88 277.95	0.53	0.32	0.60
	Sandoz omeprazole® 20mg	Cap	Generic	1 145	133.34	63.90	152 678.70	0.85	0.55	0.65
	Ulzec® 20mg	Cap	Generic	8	293.41	13.65	2 347.25	0.01	0.01	1.42
			SUBTOTAL	9 837	313.43	218.31	3 083 240.24	7.27	11.04	1.52
	Losec mups® 40mg	Tab	Innovator	588	743.16	360.47	436 977.47	0.43	1.57	3.60
			SUBTOTAL	588	743.16	360.47	436 977.47	0.43	1.57	3.60
	Losec® Infus	Inj	Innovator	8	2 017.59	1 012.60	16 140.68	0.01	0.06	9.79
			SUBTOTAL	8	2 017.59	1 012.60	16 140.68	0.01	0.06	9.79
			TOTAL	13 291			4 284 295.83	9.82	15.35	1.56

Table B3 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2004.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Pantoprazole	Pantoloc® IV 40mg	Inj	Innovator	3	935.62	1 058.55	2 806.86	0.00	0.01	4.54
			SUBTOTAL	3	935.62	1 058.55	2 806.86	0.00	0.01	4.54
	Controloc® 20mg	Tab	Innovator	2 021	209.60	77.49	423 604.07	1.49	1.52	1.02
	Pantoloc® 20mg	Tab	Innovator	3 714	198.39	67.20	736 821.54	2.74	2.64	0.96
			SUBTOTAL	5 735	202.34	71.19	1 160 425.61	4.24	4.16	0.98
	Controloc® 40mg	Tab	Innovator	3 460	347.19	146.02	1 201 266.70	2.56	4.30	1.68
	Pantoloc® 40mg	Tab	Innovator	5 068	329.04	139.62	1 667 550.95	3.74	5.97	1.60
			SUBTOTAL	8 528	336.40	142.53	2 868 817.65	6.30	10.28	1.63
			TOTAL	14 266			4 032 050.12	10.54	14.44	1.37
Rabeprazole	Pariet® 10mg	Tab	Innovator	2 113	227.18	71.07	480 035.50	1.56	1.72	1.10
			SUBTOTAL	2 113	227.18	71.07	480 035.50	1.56	1.72	1.10
	Pariet® 20mg	Tab	Innovator	4 848	376.51	159.37	1 825 301.88	3.58	6.54	1.83
			SUBTOTAL	4 848	376.51	159.37	1 825 301.88	3.58	6.54	1.83
			TOTAL	6 961			2 305 337.38	5.14	8.26	1.61

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of acid reducers for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table B4: The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Sabax cimetidine® 200mg	Amp	Generic	1	15.93	0.00	15.93	0.00	0.00	0.09
			SUBTOTAL	1	15.93	0.00	15.93	0.00	0.00	0.09
	Tagamet® 200mg	Tab	Innovator	3	79.51	56.00	238.53	0.00	0.00	0.44
	Acidown® 200mg	Tab	Generic	1	5.71	0.00	5.71	0.00	0.00	0.03
	Aci-med OTC®	Tab	Generic	1	2.47	0.00	2.47	0.00	0.00	0.01
	Adco-cimetidine® 200mg	Tab	Generic	100	23.81	15.43	2 380.82	0.11	0.01	0.13
	Bio-cimetidine® 200mg	Tab	Generic	15	12.54	7.09	188.10	0.02	0.00	0.07
	Cimlok® 200mg	Tab	Generic	177	18.47	14.52	3 269.13	0.19	0.02	0.10
	Hexamet® 200mg	Tab	Generic	27	22.69	12.54	612.61	0.03	0.00	0.12
	Lenamet® 200mg	Tab	Generic	151	17.42	9.78	2 630.92	0.16	0.02	0.10
	Lenamet OTC®	Tab	Generic	84	21.54	17.80	1 809.34	0.09	0.01	0.12
	Secadine® 200mg	Tab	Generic	4	12.56	0.03	50.24	0.00	0.00	0.07
	Rolab-cimetidine® 200mg	Tab	Generic	10	22.19	9.94	221.85	0.01	0.00	0.12
			SUBTOTAL	573	19.91	15.01	11 409.72	0.62	0.07	0.11

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
	Tagamet® 400mg	Tab	Innovator	20	118.49	213.46	2 369.70	0.02	0.01	0.65
	Aci-med® 400mg	Tab	Generic	1	6.14	0.00	6.14	0.00	0.00	0.03
	Adco-cimetidine® 400mg	Tab	Generic	560	33.14	20.17	18 557.24	0.60	0.11	0.18
	Bio-cimetidine® 400mg	Tab	Generic	40	21.90	7.91	875.96	0.04	0.01	0.12
	Cimlok® 400mg	Tab	Generic	258	25.22	17.19	6 507.02	0.28	0.04	0.14
	Cinadine® 400mg	Tab	Generic	4	48.45	26.53	193.81	0.00	0.00	0.27
	Hexamet® 400mg	Tab	Generic	209	31.55	16.51	6 594.76	0.23	0.04	0.17
	Lenamet® 400mg	Tab	Generic	709	27.95	13.99	19 815.43	0.77	0.12	0.15
	Secadine® 400mg	Tab	Generic	21	26.80	13.12	562.85	0.02	0.00	0.15
	Rolab-cimetidine® 400mg	Tab	Generic	109	30.51	14.98	3 325.08	0.12	0.02	0.17
			SUBTOTAL	1 931	30.45	28.54	58 807.99	2.09	0.35	0.17
			TOTAL	2 505			70 233.64	2.71	0.42	0.15
Nizatidine	Antizid® 150 mg	Cap	Innovator	174	174.67	94.60	30 392.10	0.19	0.18	0.96
			TOTAL	174	174.67	94.60	30 392.10	0.19	0.18	0.96

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac®	Syr	Innovator	41	207.48	171.86	8 506.77	0.04	0.05	1.14
			SUBTOTAL	41	207.48	171.86	8 506.77	0.04	0.05	1.14
	Zantac® 2ml/50mg	Inj	Innovator	119	192.51	352.98	22 908.30	0.13	0.14	1.06
			SUBTOTAL	119	192.51	352.98	22 908.30	0.13	0.14	1.06
	Zantac® 75mg	Tab	Innovator	237	63.41	42.46	15 028.37	0.26	0.09	0.35
	Gi-tak® 75mg	Tab	Generic	4	16.81	9.55	67.25	0.00	0.00	0.09
	Histak® 75 mg	Tab	Generic	114	30.12	21.30	3 433.25	0.12	0.02	0.17
	Ultak® 75mg	Tab	Generic	33	27.37	16.54	903.36	0.04	0.01	0.15
			SUBTOTAL	388	50.08	39.20	19 432.23	0.42	0.12	0.28
	Zantac® 150mg	Tab	Innovator	236	302.00	193.56	71 272.64	0.25	0.42	1.66
	Apo-ranitidine® 150mg	Tab	Generic	5	42.86	9.85	214.32	0.01	0.00	0.24
	Be-tabs ranitidine® 150mg	Tab	Generic	20	39.78	17.30	795.66	0.02	0.00	0.22
	CPL ranitidine® 150mg	Tab	Generic	13	22.90	16.77	297.67	0.01	0.00	0.13
	Histak® 150mg	Tab	Generic	1 647	42.36	19.52	69 766.33	1.78	0.42	0.23
	Ranihexal® 150mg	Tab	Generic	1 326	72.58	46.81	96 247.60	1.43	0.57	0.40
	Ultak® 150mg	Tab	Generic	1 575	41.44	18.56	65 265.53	1.70	0.39	0.23
			SUBTOTAL	4 822	63.02	76.15	303 859.75	5.21	1.81	0.35

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac® 300mg	Tab	Innovator	210	601.72	235.66	126 361.61	0.23	0.75	3.31
	Be-tabs ranitidine® 300mg	Tab	Generic	22	40.93	18.67	900.47	0.02	0.01	0.23
	CPL ranitidine® 300mg	Tab	Generic	8	29.11	12.10	232.85	0.01	0.00	0.16
	Histak® 300mg	Tab	Generic	581	36.74	13.91	21 345.87	0.63	0.13	0.20
	Ranhexal® 300mg	Tab	Generic	720	51.92	18.92	37 381.63	0.78	0.22	0.29
	Ultak® 300mg	Tab	Generic	1 195	48.59	20.90	58 063.37	1.29	0.35	0.27
			SUBTOTAL	2 736	89.29	162.61	244 285.80	2.96	1.45	0.49
	Zantac® eff 75mg	Tab	Innovator	70	69.99	35.61	4 899.48	0.08	0.03	0.39
			SUBTOTAL	70	69.99	35.61	4 899.48	0.08	0.03	0.39
	Zantac® eff 150mg	Tab	Innovator	3 448	280.53	163.22	967 280.67	3.72	5.76	1.55
			SUBTOTAL	3 448	280.53	163.22	967 280.67	3.72	5.76	1.55
	Zantac® eff 300mg	Tab	Innovator	954	506.76	193.46	483 451.69	1.03	2.88	2.79
			SUBTOTAL	954	506.76	193.46	483 451.69	1.03	2.88	2.79
			TOTAL	12 578			2 054 624.69	13.59	12.23	0.90
PPIs										
Omeprazole /amoxicillin/ clarithromycin	Losec 20 Triple pack®	Cap	Innovator	2	609.90	0.00	1 219.80	0.00	0.01	3.36
			TOTAL	2	609.90	0.00	1 219.80	0.00	0.01	3.36

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Lansoprazole	Lanzor® 15mg	Cap	Innovator	2 328	267.78	98.75	623 386.51	2.51	3.71	1.47
	Aspen Lansoprazole® 15mg	Cap	Generic	26	136.47	50.26	3 548.28	0.03	0.02	0.75
	Lansoloc® 15mg	Cap	Generic	287	120.36	55.69	34 543.52	0.31	0.21	0.66
	Lanzor® HB	Cap	Innovator	146	150.10	92.97	21 915.23	0.16	0.13	0.83
	Lansoloc® OTC	Cap	Generic	34	60.98	40.00	2 073.20	0.04	0.01	0.34
			SUBTOTAL	2 821	242.99	108.79	685 466.74	3.05	4.08	1.34
	Lanzor® 30 mg	Cap	Innovator	5 490	414.96	151.52	2 278 151.84	5.93	13.56	2.29
	Adco-Roznal® 30mg	Cap	Generic	115	163.76	61.09	18 832.65	0.12	0.11	0.90
	Aspen-lansoprazole® 30mg	Cap	Generic	36	145.03	85.28	5 221.00	0.04	0.03	0.80
	Lansoloc® 30mg	Cap	Generic	701	129.53	87.15	90 799.20	0.76	0.54	0.71
			SUBTOTAL	6 342	377.33	173.11	2 393 004.69	6.85	14.24	2.08
			TOTAL	9 163			3 078 471.43	9.80	18.32	1.85
Esomeprazole	Nexiam® 20mg	Tab	Innovator	4 560	234.24	79.62	1 068 135.80	4.93	6.36	1.29
			SUBTOTAL	4 560	234.24	79.62	1 068 135.80	4.93	6.36	1.29
	Nexiam® 40mg	Tab	Innovator	5 970	330.33	150.26	1 972 059.51	6.45	11.74	1.82
			SUBTOTAL	5 970	330.33	150.26	1 972 059.51	6.45	11.74	1.82
	Nexiam®	IV	Innovator	2	190.77	41.15	381.54	0.00	0.00	1.05
			SUBTOTAL	2	190.77	41.15	381.54	0.00	0.00	1.05
			TOTAL	10 532			3 040 576.85	11.38	18.09	1.59

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Omeprazole	Losec mups® 10mg	Tab	Innovator	870	210.53	84.81	183 159.89	0.94	1.09	1.16
	Altosec® 10mg	Cap	Generic	271	126.96	53.63	34 406.23	0.29	0.20	0.70
	Omez® 10mg	Cap	Generic	253	122.81	40.72	31 070.69	0.27	0.18	0.68
			SUBTOTAL	1 394	178.36	84.06	248 636.81	1.51	1.48	0.98
	Losec mups® 20mg	Tab	Innovator	1 349	324.97	188.09	438 381.14	1.46	2.61	1.79
	Altosec® 20mg	Cap	Generic	1 625	128.15	43.04	208 249.31	1.76	1.24	0.71
	Adco-omeprazole® 20 mg	Cap	Generic	6 320	101.93	79.16	644 191.07	6.83	3.83	0.56
	DRL-omeprazole® 20mg	Cap	Generic	14	103.28	45.15	1 445.89	0.02	0.01	0.57
	Nozer® 20mg	Cap	Generic	37	109.02	43.48	4 033.57	0.04	0.02	0.60
	Omez® 20mg	Cap	Generic	873	115.99	52.35	101 256.28	0.94	0.60	0.64
	Omiloc® 20mg	Cap	Generic	259	104.23	40.96	26 996.38	0.28	0.16	0.57
	Sandoz omeprazole® 20mg	Cap	Generic	3458	141.83	49.41	490 432.86	3.74	2.92	0.78
			SUBTOTAL	13 935	137.42	106.49	1 914 986.50	15.05	11.40	0.76
	Losec mups® 40mg	Tab	Innovator	289	843.63	292.91	243 808.18	0.31	1.45	4.65
			SUBTOTAL	289	843.63	292.91	243 808.18	0.31	1.45	4.65
	Losec® Infus	Inj	Innovator	9	526.36	543.70	4 737.23	0.01	0.03	2.90
			SUBTOTAL	9	526.36	543.70	4 737.23	0.01	0.03	2.90
			TOTAL	15 627			2 412 168.72	16.88	14.35	0.85
Pantoprazole	Pantoloc® IV 40mg	Inj	Innovator	9	159.70	60.03	1 437.31	0.01	0.01	0.88
			SUBTOTAL	9	159.70	60.03	1 437.31	0.01	0.01	0.88
	Controloc® 20mg	Tab	Innovator	1 461	198.49	68.04	290 000.59	1.58	1.73	1.09
	Pantoloc® 20mg	Tab	Innovator	1 416	172.11	44.16	243 702.61	1.53	1.45	0.95
			SUBTOTAL	2 877	185.51	59.03	533 703.20	3.11	3.18	1.02

Table B4 (Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2005.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Pantoprazole	Controloc® 40mg	Tab	Innovator	2 979	359.81	110.35	1 071 883.15	3.22	6.38	1.98
	Pantoloc® 40mg	Tab	Innovator	2 390	290.04	101.44	693 198.97	2.58	4.13	1.60
			SUBTOTAL	5 369	328.75	111.97	1 765 082.12	5.80	10.50	1.81
			TOTAL	8 255			2 300 222.63	8.92	13.69	1.53
Rabeprazole	Pariet® 10mg	Tab	Innovator	1 006	246.65	75.46	248 130.57	1.09	1.48	1.36
			SUBTOTAL	1 006	246.65	75.46	248 130.57	1.09	1.48	1.36
	Pariet® 20mg	Tab	Innovator	4 073	422.63	172.19	1 721 376.37	4.40	10.24	2.33
			SUBTOTAL	4 073	422.63	172.19	1 721 376.37	4.40	10.24	2.33
			TOTAL	5 079			1 969 506.94	5.49	11.72	2.14

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of acid reducers for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table B5: The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Cimetidine	Acidown® 200mg	Tab	Generic	2	12.85	6.06	25.69	0.00	0.00	0.07
	Adco-cimetidine® 200mg	Tab	Generic	39	25.72	11.81	1 002.93	0.07	0.01	0.15
	Bio-cimetidine® 200mg	Tab	Generic	3	5.73	0.58	17.18	0.01	0.00	0.03
	Cimlok® 200mg	Tab	Generic	66	18.86	10.31	1 244.52	0.11	0.01	0.11
	Hexamet® 200mg	Tab	Generic	7	23.96	5.99	167.73	0.01	0.00	0.14
	Lenamet® 200mg	Tab	Generic	49	23.26	22.93	1 139.95	0.08	0.01	0.13
	Lenamet OTC®	Tab	Generic	8	13.65	8.37	109.18	0.01	0.00	0.08
	Secadine® 200mg	Tab	Generic	2	6.37	2.02	12.73	0.00	0.00	0.04
	Rolab-cimetidine® 200mg	Tab	Generic	6	37.21	16.60	223.24	0.01	0.00	0.21
			SUBTOTAL	182	21.67	15.63	3 943.15	0.31	0.04	0.12
	Tagamet® 400mg	Tab	Innovator	3	340.64	276.44	1 021.92	0.01	0.01	1.94
	Adco-cimetidine® 400mg	Tab	Generic	440	32.18	19.01	14 160.90	0.74	0.14	0.18
	Cimlok® 400mg	Tab	Generic	47	15.84	10.03	744.66	0.08	0.01	0.09
	Cinadine® 400mg	Tab	Generic	2	124.54	13.98	249.07	0.00	0.00	0.71
	Hexamet® 400mg	Tab	Generic	54	29.16	17.71	1 574.83	0.09	0.02	0.17
	Lenamet® 400mg	Tab	Generic	254	30.96	13.22	7 864.51	0.43	0.08	0.18
	Secadine® 400mg	Tab	Generic	1	20.89	0.00	20.89	0.00	0.00	0.12
	Rolab-cimetidine® 400mg	Tab	Generic	70	39.51	13.68	2 765.40	0.12	0.03	0.22
			SUBTOTAL	871	32.61	28.56	28 402.18	1.47	0.27	0.19
			TOTAL	1 053			32 345.33	1.78	0.31	0.17

Table B5(Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Nizatidine	Antizid® 150 mg	Cap	Innovator	95	120.87	41.63	11 482.42	0.16	0.11	0.69
			TOTAL	95	120.87	41.63	11 482.42	0.16	0.11	0.69
Ranitidine	Zantac®	Syr	Innovator	15	261.31	158.69	3 919.60	0.03	0.04	1.49
			SUBTOTAL	15	261.31	158.69	3 919.60	0.03	0.04	1.49
	Zantac® 2ml/50mg	Inj	Innovator	81	169.98	263.67	13 768.47	0.14	0.13	0.97
	CPL ranitidine®	Inj	Generic	1	46.48	0.00	46.48	0.00	0.00	0.26
			SUBTOTAL	82	168.48	262.39	13 814.95	0.14	0.13	0.96
	Zantac® 75mg	Tab	Innovator	136	74.00	39.49	10 064.36	0.23	0.10	0.42
	Histak® 75 mg	Tab	Generic	38	30.17	18.90	1 146.64	0.06	0.01	0.17
	Ultak® 75mg	Tab	Generic	33	21.50	14.12	709.59	0.06	0.01	0.12
			SUBTOTAL	207	57.59	40.52	11 920.59	0.35	0.11	0.33
	Zantac® 150mg	Tab	Innovator	81	402.28	251.99	32 584.76	0.14	0.31	2.29
	Be-tabs ranitidine® 150mg	Tab	Generic	1	35.45	0.00	35.45	0.00	0.00	0.20
	CPL ranitidine® 150mg	Tab	Generic	1	6.95	0.00	6.95	0.00	0.00	0.04
	Histak® 150mg	Tab	Generic	1 618	43.25	17.99	69 983.20	2.74	0.67	0.25
	Ranhexal® 150mg	Tab	Generic	1 154	91.01	53.36	105 029.88	1.95	1.01	0.52
	Ranit® 150mg	Tab	Generic	4	51.81	2.84	207.23	0.01	0.00	0.29
	Ultak® 150mg	Tab	Generic	543	45.88	18.74	24 911.64	0.92	0.24	0.26
			SUBTOTAL	3 402	68.42	76.69	232 759.11	5.75	2.24	0.39

Table B5(Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
H₂RA										
Ranitidine	Zantac [®] 300mg	Tab	Innovator	42	548.29	381.47	23 028.05	0.07	0.22	3.12
	CPL ranitidine [®] 300mg	Tab	Generic	8	36.48	29.71	291.87	0.01	0.00	0.21
	Histak [®] 300mg	Tab	Generic	739	41.79	11.26	30 884.77	1.25	0.30	0.24
	Ranihexal [®] 300mg	Tab	Generic	488	57.62	19.25	28 116.88	0.82	0.27	0.33
	Ranit [®] 300mg	Tab	Generic	2	38.44	6.15	76.88	0.00	0.00	0.22
	Ultak [®] 300mg	Tab	Generic	611	54.00	26.76	32 994.56	1.03	0.32	0.31
			SUBTOTAL	1 890	61.06	94.78	115 393.01	3.19	1.11	0.35
	Zantac [®] eff 75mg	Tab	Innovator	94	99.85	60.94	9 386.17	0.16	0.09	0.57
			SUBTOTAL	94	99.85	60.94	9 386.17	0.16	0.09	0.57
	Zantac [®] eff 150mg	Tab	Innovator	3 158	284.55	169.79	898 595.29	5.34	8.65	1.62
			SUBTOTAL	3 158	284.55	169.79	898 595.29	5.34	8.65	1.62
	Zantac [®] eff 300mg	Tab	Innovator	804	472.36	199.39	379 779.07	1.36	3.65	2.69
			SUBTOTAL	804	472.36	199.39	379 779.07	1.36	3.65	2.69
			TOTAL	9 652			1 665 567.79	16.32	16.02	0.98
PPIs										
Lansoprazole	Lanzor [®] 15mg	Cap	Innovator	269	282.10	126.41	75 885.37	0.45	0.73	1.61
	Aspen Lansoprazole [®] 15mg	Cap	Generic	104	90.34	92.36	9 395.47	0.18	0.09	0.51
	Lansoloc [®] 15mg	Cap	Generic	683	84.65	93.15	57 817.01	1.15	0.56	0.48
	Lanzor [®] HB	Cap	Innovator	8	158.28	116.40	1 266.23	0.01	0.01	0.90
	Lansoloc [®] OTC	Cap	Generic	79	56.23	33.81	4 442.06	0.13	0.04	0.32
			SUBTOTAL	1 143	130.19	130.64	148 806.14	1.93	1.43	0.74

Table B5(Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Lansoprazole	Lanzor® 30 mg	Cap	Innovator	744	393.64	206.99	292 870.45	1.26	2.82	2.24
	Adco-Roznal® 30mg	Cap	Generic	712	220.45	31.93	156 959.55	1.20	1.51	1.25
	Aspen-lansoprazole® 30mg	Cap	Generic	483	61.23	94.44	29 572.26	0.82	0.28	0.35
	Lansoloc® 30mg	Cap	Generic	2 331	83.56	109.23	194 788.45	3.94	1.87	0.48
			SUBTOTAL	4 270	157.89	178.60	674 190.71	7.22	6.49	0.90
			TOTAL	5 413			822 996.85	9.15	7.92	0.87
Esomeprazole	Nexiam® 20mg	Tab	Innovator	1 375	288.14	90.59	396 192.31	2.32	3.81	1.64
			SUBTOTAL	1 375	288.14	90.59	396 192.31	2.32	3.81	1.64
	Nexiam® 40mg	Tab	Innovator	2 886	429.50	126.91	1 239 530.07	4.88	11.93	2.44
			SUBTOTAL	2 886	429.50	126.91	1 239 530.07	4.88	11.93	2.44
	Nexiam®	IV	Innovator	13	217.79	19.62	2 831.33	0.02	0.03	1.24
			SUBTOTAL	13	217.79	19.62	2 831.33	0.02	0.03	1.24
Omeprazole			TOTAL	4 274			1 638 553.71	7.22	15.76	2.18
	Losec mups® 10mg	Tab	Innovator	212	194.43	166.41	41 220.13	0.36	0.40	1.11
	Altosec® 10mg	Cap	Generic	317	135.69	47.13	43 013.28	0.54	0.41	0.77
	Omez® 10mg	Cap	Generic	63	137.46	38.38	8 660.28	0.11	0.08	0.78
			SUBTOTAL	592	156.92	109.61	92 893.69	1.00	0.89	0.89

Table B5(Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Omeprazole	Losec mups® 20mg	Tab	Innovator	491	378.98	197.13	186 080.68	0.83	1.79	2.16
	Altosec® 20mg	Cap	Generic	3 671	141.56	42.36	519 660.34	6.21	5.00	0.81
	Adco-omeprazole® 20 mg	Cap	Generic	4 797	155.03	46.87	743 695.42	8.11	7.16	0.88
	DRL-omeprazole® 20mg	Cap	Generic	24	140.53	24.75	3 372.71	0.04	0.03	0.80
	Lokit® 20mg	Cap	Generic	152	140.89	35.35	21 415.47	0.26	0.21	0.80
	Nozer® 20mg	Cap	Generic	28	90.95	41.34	2 546.62	0.05	0.02	0.52
	Omez® 20mg	Cap	Generic	230	127.79	54.86	29 390.92	0.39	0.28	0.73
	Omiloc® 20mg	Cap	Generic	195	165.23	60.62	32 219.72	0.33	0.31	0.94
	Sandoz omeprazole® 20mg	Cap	Generic	3 454	152.61	44.83	527 126.51	5.84	5.07	0.87
			SUBTOTAL	13 042	158.37	73.40	2 065 508.39	22.05	19.87	0.90
	Losec mups® 40mg	Tab	Innovator	151	845.01	284.88	127 596.25	0.26	1.23	4.81
	Omez® 40mg	Cap	Generic	2	209.31	98.66	418.61	0.00	0.00	1.19
			SUBTOTAL	153	836.70	292.23	128 014.86	0.26	1.23	4.76
	Losec® Infus	Inj	Innovator	21	1 005.62	1 921.70	21 118.00	0.04	0.20	5.72
			SUBTOTAL	21	1 005.62	1 921.70	21 118.00	0.04	0.20	5.72
			TOTAL	13 808			2 307 534.94	23.34	22.20	0.95

Table B5(Continued): The prevalence, average cost and total cost of individual H₂RAs and PPIs for 2006.

Active ingredient	Trade name	DF	Innovator/ Generic	Prevalence	Average cost per medicine item (R)	Std dev ±	Total cost (R)	Prevalence %	Cost %	CPI
PPIs										
Pantoprazole	Pantoloc® IV 40mg	Inj	Innovator	5	176.63	6.73	883.16	0.01	0.01	1.01
			SUBTOTAL	5	176.63	6.73	883.16	0.01	0.01	1.01
	Controloc® 20mg	Tab	Innovator	526	205.17	59.44	107 919.44	0.89	1.04	1.17
	Pantoloc® 20mg	Tab	Innovator	179	184.32	56.98	32 993.20	0.30	0.32	1.05
	Topzole® 20mg	Tab	Generic	304	184.24	59.99	56 009.53	0.51	0.54	1.05
			SUBTOTAL	1 009	195.17	60.03	196 922.17	1.71	1.89	1.11
	Controloc® 40mg	Tab	Innovator	1 185	364.03	90.78	431 381.45	2.00	4.15	2.07
	Pantoloc® 40mg	Tab	Innovator	577	364.33	133.95	210 220.89	0.98	2.02	2.07
	Topzole® 40mg	Tab	Generic	1 041	320.51	83.54	333 651.34	1.76	3.21	1.82
			SUBTOTAL	2 803	347.93	101.02	975 253.68	4.74	9.38	1.98
			TOTAL	3 817			1 173 059.01	6.45	11.29	1.75
Rabeprazole	Pariet® 10mg	Tab	Innovator	416	292.91	85.78	121 850.73	0.70	1.17	1.67
			SUBTOTAL	416	292.91	85.78	121 850.73	0.70	1.17	1.67
	Pariet® 20mg	Tab	Innovator	2 789	468.90	154.24	1 307 772.69	4.71	12.58	2.67
			SUBTOTAL	2 789	468.90	154.24	1 307 772.69	4.71	12.58	2.67
			TOTAL	3 621			1 551 474.15	6.12	14.93	2.44

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of acid reducing medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of acid reducers for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table C1: The top 20 H₂RAs for 2001.

Tradename	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Zantac [®] eff 150mg	Tab	1 501	11.91	238 666.59	10.95	0.92
Lenamet [®] 400mg	Tab	1 191	9.45	208 802.35	9.58	1.01
Ranhexal [®] 150mg	Tab	1 208	9.58	195 984.17	8.99	0.94
Adco-cimetidine [®] 400mg	Tab	978	7.76	190 379.58	8.73	1.13
Ranhexal [®] 300mg	Tab	542	4.30	126 455.41	5.80	1.35
Zantac [®] 150mg	Tab	523	4.15	125 561.22	5.76	1.39
Histak [®] 150mg	Tab	494	3.92	112 031.23	5.14	1.31
Hexamet [®] 400mg	Tab	602	4.78	108 116.84	4.96	1.04
Ultak [®] 150mg	Tab	809	6.42	91 555.24	4.20	0.65
Zantac [®] eff 300mg	Tab	206	1.63	87 994.10	4.04	2.47
Zantac [®] 75mg	Tab	908	7.20	76 055.94	3.49	0.48
Zantac [®] 300mg	Tab	187	1.48	58 489.70	2.68	1.81
Histak [®] 300mg	Tab	216	1.71	54 995.15	2.52	1.47
Apo-ranitidine [®] 150mg	Tab	202	1.60	48 976.69	2.25	1.40
Cimlok [®] 400mg	Tab	264	2.09	45 444.12	2.08	1.00
Lenamet [®] 200mg	Tab	489	3.88	40 928.18	1.88	0.48
Ulcaid [®] 150mg	Tab	189	1.50	37 988.69	1.74	1.16
Garec-ranitidine [®] 150mg	Tab	185	1.47	35 837.66	1.64	1.12
Ultak [®] 300mg	Tab	221	1.75	32 692.67	1.50	0.86
Cinadine [®] 400mg	Tab	163	1.29	28 799.91	1.32	1.02

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of H₂RA medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of H₂RA for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table C2: The top 20 H₂RAs for 2002.

Tradename	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Zantac [®] eff 150mg	Tab	1 838	11.38	366 239.26	13.34	1.17
Ranhexal [®] 150mg	Tab	1 881	11.65	298 529.15	10.87	0.93
Lenamet [®] 400mg	Tab	1 448	8.97	249 644.91	9.09	1.01
Histak [®] 150mg	Tab	971	6.01	201 727.07	7.35	1.22
Ultak [®] 150mg	Tab	1 459	9.04	175 934.79	6.41	0.71
Adco-cimetidine [®] 400mg	Tab	896	5.55	169 053.69	6.16	1.11
Zantac [®] eff 300mg	Tab	378	2.34	162 142.35	5.90	2.52
Zantac [®] 150mg	Tab	538	3.33	134 206.54	4.89	1.47
Hexamet [®] 400mg	Tab	691	4.28	128 044.82	4.66	1.09
Ultak [®] 300mg	Tab	587	3.64	103 186.42	3.76	1.03
Zantac [®] 300mg	Tab	260	1.61	95 103.76	3.46	2.15
Ranhexal [®] 300mg	Tab	534	3.31	91 354.95	3.33	1.01
Zantac [®] 75mg	Tab	1 006	6.23	80 646.53	2.94	0.47
Cimlok [®] 400mg	Tab	344	2.13	60 326.04	2.20	1.03
Histak [®] 300mg	Tab	296	1.83	51 524.28	1.88	1.02
Antizid [®] 150mg	Cap	183	1.13	45 416.38	1.65	1.46
Lenamet [®] 200mg	Tab	502	3.11	37 036.64	1.35	0.43
Pepcid [®] 40mg	Tab	67	0.41	30 859.96	1.12	2.71
Secadine [®] 400mg	Tab	152	0.94	27 454.81	1.00	1.06
Adco-cimetidine [®] 200mg	Tab	275	1.70	21 747.61	0.79	0.47

DF- Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of H₂RA medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of H₂RA for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table C3: The top 20 H₂RAs for 2004.

Tradename	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Zantac [®] eff 150mg	Tab	2 662	12.76	692 443.26	25.61	2.01
Zantac [®] eff 300mg	Tab	652	3.13	324 468.17	12.00	3.84
Ranixhexal [®] 150mg	Tab	2 297	11.01	206 136.75	7.62	0.69
Histak [®] 150mg	Tab	2 586	12.40	182 445.01	6.75	0.54
Ultak [®] 150mg	Tab	2 211	10.60	157 546.99	5.83	0.55
Zantac [®] 300mg	Tab	282	1.35	142 722.54	5.28	3.90
Zantac [®] 150mg	Tab	445	2.13	142 127.15	5.26	2.46
Ultak [®] 300mg	Tab	1 023	4.90	120 667.13	4.46	0.91
Lenamet [®] 400mg	Tab	1 569	7.52	118 329.90	4.38	0.58
Ranixhexal [®] 300mg	Tab	1 077	5.16	101 866.79	3.77	0.73
Adco-cimetidine [®] 400mg	Tab	926	4.44	78 766.18	2.91	0.66
Histak [®] 300mg	Tab	714	3.42	76 165.51	2.82	0.82
Pepcid [®] 40mg	Tab	107	0.51	51 851.67	1.92	3.74
Antizid [®] 150mg	Cap	233	1.12	51 674.85	1.91	1.71
Cimlok [®] 400mg	Tab	515	2.47	39 674.58	1.47	0.59
Hexamet [®] 400mg	Tab	449	2.15	36 147.28	1.34	0.62
Zantac [®] 75mg	Tab	327	1.57	20 551.34	0.76	0.48
Rolab-cimetidine [®] 400mg	Tab	177	0.85	18 106.49	0.67	0.79
Histak [®] 75mg	Tab	395	1.89	15 635.09	0.58	0.31
Lenamet [®] 200mg	Tab	461	2.21	15 634.50	0.58	0.26

DF - Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of H₂RA medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of H₂RA for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table C4: The top 20 H₂RAs for 2005.

Tradename	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Zantac [®] eff 150mg	Tab	3 448	22.60	967 280.67	44.88	1.99
Zantac [®] eff 300mg	Tab	954	6.25	483 451.69	22.43	3.59
Zantac [®] 300mg	Tab	210	1.38	126 361.61	5.86	4.26
Ranhexal [®] 150mg	Tab	1 326	8.69	96 247.60	4.47	0.51
Zantac [®] 150mg	Tab	236	1.55	71 272.64	3.31	2.14
Histak [®] 150mg	Tab	1 647	10.80	69 766.33	3.24	0.30
Ultak [®] 150mg	Tab	1 575	10.32	65 265.53	3.03	0.29
Ultak [®] 300mg	Tab	1 195	7.83	58 063.37	2.69	0.34
Ranhexal [®] 300mg	Tab	720	4.72	37 381.63	1.73	0.37
Antizid [®] 150mg	Cap	174	1.14	30 392.10	1.41	1.24
Zantac [®]	Inj	119	0.78	22 908.30	1.06	1.36
Histak [®] 300mg	Tab	581	3.81	21 345.87	0.99	0.26
Lenamet [®] 400mg	Tab	709	4.65	19 815.43	0.92	0.20
Adco-cimetidine [®] 400mg	Tab	560	3.67	18 557.24	0.86	0.23
Zantac [®] 75mg	Tab	237	1.55	15 028.37	0.70	0.45
Zantac [®]	Syr	41	0.27	8 506.77	0.39	1.47
Hexamet [®] 400mg	Tab	209	1.37	6 594.76	0.31	0.22
Cimlok [®] 400mg	Tab	258	1.69	6 507.02	0.30	0.18
Zantac [®] eff 75mg	Tab	70	0.46	4 899.48	0.23	0.50
Histak [®] 75mg	Tab	114	0.75	3 433.25	0.16	0.21

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of H₂RA medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of H₂RA for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table C5: The top 20 H₂RAs for 2006.

Tradename	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Zantac [®] eff 150mg	Tab	3 158	29.24	898 595.29	52.57	1.80
Zantac [®] eff 300mg	Tab	804	7.44	379 779.07	22.22	2.98
Ranixhexal [®] 150mg	Tab	1 154	10.69	105 029.88	6.14	0.58
Histak [®] 150mg	Tab	1 618	14.98	69 983.20	4.09	0.27
Ultak [®] 300mg	Tab	611	5.66	32 994.56	1.93	0.34
Zantac [®] 150mg	Tab	81	0.75	32 584.76	1.91	2.54
Histak [®] 300mg	Tab	739	6.84	30 884.77	1.81	0.26
Ranixhexal [®] 300mg	Tab	488	4.52	28 116.88	1.64	0.36
Ultak [®] 150mg	Tab	543	5.03	24 911.64	1.46	0.29
Zantac [®] 300mg	Tab	42	0.39	23 028.05	1.35	3.46
Adco-cimetidine [®] 400mg	Tab	440	4.07	14 160.90	0.83	0.20
Zantac [®]	Inj	81	0.75	13 768.47	0.81	1.07
Antizid [®] 150mg	Cap	95	0.88	11 482.47	0.67	0.76
Zantac [®] 75mg	Tab	136	1.26	10 064.36	0.59	0.47
Zantac [®] eff 75mg	Tab	94	0.87	9 386.17	0.55	0.63
Lenamet [®] 400mg	Tab	254	2.35	7 864.51	0.46	0.20
Zantac [®]	Syr	15	0.14	3 919.60	0.23	1.65
Rolab-cimetidine [®] 400mg	Tab	70	0.65	2 765.40	0.16	0.25
Hexamet [®] 400mg	Tab	54	0.50	1 574.83	0.09	0.18
Cimlok [®] 200mg	Tab	66	0.61	1 244.52	0.07	0.12

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of H₂RA medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of H₂RA for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table D1: The top 20 PPIs for 2001.

Trade name	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Lanzor [®] 30mg	Cap	9 704	24.42	3 866 295.47	27.11	1.11
Losec mups [®] 20mg	Tab	8 361	21.04	3 456 060.37	24.24	1.15
Lanzor [®] 15mg	Cap	5 151	12.97	1 480 051.48	10.38	0.80
Pantoloc [®] 40mg	Tab	3 384	8.52	1 324 728.59	9.29	1.09
Pariet [®] 20mg	Tab	3 703	9.32	1 180 139.47	8.28	0.89
Losec mups [®] 10mg	Tab	3 354	8.44	959 827.11	6.73	0.80
Controloc [®] 40mg	Tab	2 133	5.37	793 267.95	5.56	1.04
Pariet [®] 10mg	Tab	2 231	5.62	520 978.63	3.65	0.65
Losec mups [®] 40mg	Tab	303	0.76	191 060.01	1.34	1.76
Losec 20mg triple pack	Cap	266	0.67	180 572.15	1.27	1.89
Ulzec [®] 20mg	Cap	518	1.30	158 061.25	1.11	0.85
Pantoloc [®] 20mg	Tab	418	1.05	104 308.25	0.73	0.70
Ulzec [®] 10mg	Cap	153	0.39	32 240.29	0.23	0.59
Controloc [®] 20mg	Tab	50	0.13	12 404.91	0.09	0.69
Pantoloc [®] IV	Inj	1	0.00	279.69	0.00	0.78

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of PPIs medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of PPIs for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table D2: The top 20 PPIs for 2002.

Trade name	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Lanzor [®] 30mg	Cap	10 643	19.58	4 736 747.05	23.39	1.20
Losec mups [®] 20mg	Tab	7 452	13.71	3 261 315.59	16.11	1.18
Lanzor [®] 15mg	Cap	6 322	11.63	2 072 788.25	10.24	0.88
Pariet [®] 20mg	Tab	4 401	8.09	1 680 621.53	8.30	1.03
Nexiam [®] 40mg	Tab	4 060	7.47	1 494 997.59	7.38	0.99
Pantoloc [®] 40mg	Tab	3 027	5.57	1 260 234.52	6.22	1.12
Ulzec [®] 20mg	Cap	3 971	7.30	1 225 733.21	6.05	0.83
Losec mups [®] 10mg	Tab	3 336	6.14	1 010 473.75	4.99	0.81
Controloc [®] 40mg	Tab	2 510	4.62	988 109.56	4.88	1.06
Pariet [®] 10mg	Tab	2 864	5.27	825 553.31	4.08	0.77
Nexiam [®] 20mg	Tab	1 924	3.54	538 666.27	2.66	0.75
Pantoloc [®] 20mg	Tab	1 297	2.39	329 373.03	1.63	0.68
Ulzec [®] 10mg	Cap	1 380	2.54	300 858.80	1.49	0.59
Losec 20mg triple pack	Cap	278	0.51	205 806.22	1.02	1.99
Controloc [®] 20mg	Tab	717	1.32	179 203.19	0.89	0.67
Losec mups [®] 40mg	Tab	186	0.34	137 299.35	0.68	1.98
Pantoloc [®] IV	Inj	1	0.00	330.84	0.00	0.89

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of PPIs medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of PPIs for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table D3: The top 20 PPIs for 2004.

Trade name	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Lanzor [®] 30mg	Cap	10 574	14.83	4 091 488.46	18.41	1.24
Nexiam [®] 40mg	Tab	10 360	14.53	3 430 848.83	15.43	1.06
Losec mups [®] 20mg	Tab	6 437	9.03	2 697 546.33	12.14	1.34
Nexiam [®] 20mg	Tab	8 972	12.59	2 155 314.25	9.70	0.77
Lanzor [®] 15mg	Cap	6 742	9.46	1 889 423.35	8.50	0.90
Pariet [®] 20mg	Tab	4 848	6.80	1 825 301.88	8.21	1.21
Pantoloc [®] 40mg	Tab	5 068	7.11	1 667 550.95	7.50	1.06
Controloc [®] 40mg	Tab	3 460	4.85	1 201 266.70	5.40	1.11
Pantoloc [®] 20mg	Tab	3 714	5.21	736 821.54	3.31	0.64
Losec mups [®] 10mg	Tab	2 746	3.85	734 372.36	3.30	0.86
Pariet [®] 10mg	Tab	2 113	2.96	480 035.50	2.16	0.73
Losec mups [®] 40mg	Tab	588	0.82	436 977.47	1.97	2.38
Controloc [®] 20mg	Tab	2 021	2.84	423 604.07	1.91	0.67
Sandoz omeprazole [®] 20mg	Cap	1 145	1.61	152 678.70	0.69	0.43
Adco omeprazole [®] 20mg	Cap	1 535	2.15	142 390.01	0.64	0.30
Omez [®] 20mg	Cap	712	1.00	88 277.95	0.40	0.40
Losec [®] 20mg triple pack	Cap	46	0.06	31 132.77	0.14	2.17
Losec [®] Infusus	Inj	8	0.01	16 140.68	0.07	6.47
Omez [®] 10mg	Cap	106	0.15	12 359.68	0.06	0.37
Lanzor [®] HB	Cap	67	0.09	8 833.42	0.04	0.42

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of PPIs medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of PPIs for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table D4: The top 20 PPIs for 2005.

Trade name	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Lanzor® 30mg	Cap	5 490	11.28	2 278 151.84	17.80	1.58
Nexiam® 40mg	Tab	5 970	12.27	1 972 059.51	15.40	1.26
Pariet® 20mg	Tab	4 073	8.37	1 721 376.37	13.45	1.61
Controloc® 40mg	Tab	2 979	6.12	1 071 883.15	8.37	1.37
Nexiam® 20mg	Tab	4 560	9.37	1 068 135.80	8.34	0.89
Pantoloc® 40mg	Tab	2 390	4.91	693 198.97	5.41	1.10
Adco-Omeprazole® 20mg	Cap	6 320	12.99	644 191.07	5.03	0.39
Lanzor® 15mg	Cap	2 328	4.78	623 386.51	4.87	1.02
Sandoz Omeprazole® 20mg	Cap	3 458	7.11	490 432.86	3.83	0.54
Losec mups® 20mg	Tab	1 349	2.77	438 381.14	3.42	1.24
Controloc® 20mg	Tab	1 461	3.00	290 000.59	2.27	0.75
Pariet® 10mg	Tab	1 006	2.07	248 130.57	1.94	0.94
Losec mups® 40mg	Tab	289	0.59	243 808.18	1.90	3.21
Pantoloc® 20mg	Tab	1 416	2.91	243 702.61	1.90	0.65
Altosec® 20mg	Cap	1 625	3.34	208 249.31	1.63	0.49
Losec mups® 10mg	Tab	870	1.79	183 159.89	1.43	0.80
Omez® 20mg	Cap	873	1.79	101 256.28	0.79	0.44
Lansoloc® 30mg	Cap	701	1.44	90 799.20	0.71	0.49
Lansoloc® 15mg	Cap	287	0.59	34 543.52	0.27	0.46
Altosec® 10mg	Cap	271	0.56	34 406.23	0.27	0.48

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of PPIs medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of PPIs for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table D5: The top 20 PPIs for 2006.

Trade name	DF	Prevalence	Prevalence %	Total cost (R)	Cost %	CPI
Pariet® 20mg	Tab	2 789	9.14	1 307 772.69	17.74	1.94
Nexiam® 40mg	Tab	2 886	9.46	1 239 530.07	16.81	1.78
Adco-Omeprazole® 20mg	Cap	4 797	15.72	743 695.42	10.09	0.64
Sandoz Omeprazole® 20mg	Cap	3 454	11.32	527 126.51	7.15	0.63
Altosec® 20mg	Cap	3 671	12.03	519 660.34	7.05	0.59
Controloc® 40mg	Tab	1 185	3.88	431 381.45	5.85	1.51
Nexiam® 20mg	Tab	1 375	4.51	396 192.31	5.37	1.19
Topzole® 40mg	Tab	1 041	3.41	333 651.34	4.53	1.33
Lanzor® 30mg	Cap	744	2.44	292 870.45	3.97	1.63
Pantoloc® 40mg	Tab	577	1.89	210 220.89	2.85	1.51
Lansoloc® 30mg	Cap	2 331	7.64	194 788.45	2.64	0.35
Losec mups® 20mg	Tab	491	1.61	186 080.68	2.52	1.57
Adco-Roznal® 30mg	Cap	712	2.33	156 959.55	2.13	0.91
Losec mups® 40mg	Tab	151	0.49	127 596.25	1.73	3.50
Pariet® 10mg	Tab	416	1.36	121 850.73	1.65	1.21
Controloc® 20mg	Tab	526	1.72	107 919.44	1.46	0.85
Lanzor® 15mg	Cap	269	0.88	75 885.37	1.03	1.17
Lansoloc® 15mg	Cap	683	2.24	57 817.01	0.78	0.35
Topzole® 40mg	Tab	304	1.00	56 009.53	0.76	0.76
Altosec® 10mg	Cap	317	1.04	43 013.28	0.58	0.56

DF – Dosage form

Prevalence % - The number of medicine items claimed (prevalence) for the specific period (year) divided by the total number of PPIs medicine items claimed for the corresponding year multiplied by hundred (refer to table 5.2).

Cost% - The cost of medicine items claimed for the specific period (year) divided by the total cost of PPIs for the corresponding year multiplied by hundred (refer to table 5.2).

CPI – The cost % divided by the prevalence % (refer to section 4.6.4).

Table E1: Prevalence of acid reducing medicine according to innovator and generic.

Category	Innovator/ Generic	2001		2002		2004		2005		2006	
		Prevalence	%	Prevalence	%	Prevalence	%	Prevalence	%	Prevalence	%
Antacids	Innovator/	22 709	92.04	29 275	89.91	33 404	86.97	19 867	79.26	11 854	74.65
	Generic	1 965	7.96	3 285	10.1	5 005	13.03	5 199	20.74	4 025	25.35
	TOTAL	24 674	100.00	32 560	100.00	38 409	100.00	25 066	100.00	15 879	100.00
H ₂ RA	Innovator/	3 573	28.34	4 386	27.16	5 081	24.36	5 512	36.13	4 509	41.75
	Generic	9 033	71.65	11 761	72.84	15 780	75.64	9 745	63.87	6 291	58.25
	TOTAL	12 606	100.00	16 147	100.00	20 861	100.00	15 257	100.00	10 800	100.00
PPI	Innovator/	39 059	98.31	49 018	90.16	67 767	95.07	34 349	70.59	11 847	38.82
	Generic	671	1.69	5 351	9.84	3 512	4.93	14 309	29.41	18 670	61.18
	TOTAL	39 730	100.00	54 369	100.00	71 279	100.00	48 658	100.00	30 517	100.00
Cytoprotective agents	Innovator/	3 763	100.00	4 561	100	4 852	100.00	3 584	100	1 961	100.00
	Generic	0	0.00	0	0.00	0	0.00	0	0	0	0.00
	TOTAL	3 763	100.00	4 561	100.00	4 852	100.00	3 584	100.00	1 961	100.00
Total acid reducers	Innovator/	69 104	85.55	87 240	81.05	111 104	82.06	63 312	68.40	30 171	51.00
	Generic	11 669	14.45	20 397	18.95	24 297	17.94	29 253	31.60	28 986	49.00
	TOTAL	80 773	100.00	107 637	100.00	135 401	100.00	92 565	100.00	59 157	100.00

% - The number of medicine items claimed for the specific period (year) divided by the total number of medicine items claimed for the corresponding year multiplied by hundred.

Table F1: Combination therapy for the eradication of *H. pylori*, classified as two-drug regimen with three active ingredients, for the five study years.

Year	Active ingredient	Active ingredient	Active ingredient	Prevalence	Average cost (R) per combination	Std dev ±	Total cost
Clarithromycin/PPI							
2001	Clarithromycin	Lansoprazole	Lansoprazole	1	321.37	0.00	321.37
2002	Clarithromycin	Lansoprazole	Clarithromycin	1	986.16	0.00	986.16
		Esomeprazole	Esomeprazole	7	1 052.45	341.49	7 367.17
			Omeprazole	2	1 187.28	29.90	2 374.55
		Lansoprazole	Lansoprazole	2	659.75	67.73	1 319.49
			Omeprazole	1	700.62	0.00	700.62
			Pantoprazole	1	1 067.95	0.00	1 067.95
		Omeprazole	Omeprazole	2	1 426.78	386.14	2 853.56
			Pantoprazole	1	1 122.33	0.00	1 122.33
		Pantoprazole	Pantoprazole	1	1 064.47	0.00	1 064.47
		Rabeprazole	Rabeprazole	2	818.16	265.40	1 636.31
2004	Clarithromycin	Esomeprazole	Esomeprazole	7	574.24	127.44	4 019.67
			Pantoprazole	1	439.61	0.00	439.61
		Lansoprazole	Lansoprazole	5	1 329.50	346.97	6 647.50
		Omeprazole	Omeprazole	3	838.95	433.05	2 516.84
			Pantoprazole	1	919.24	0.00	919.24
			Rabeprazole	1	1 542.60	0.00	1 542.60
		Pantoprazole	Pantoprazole	1	548.99	0.00	548.99
2005	Clarithromycin	Esomeprazole	Clarithromycin	2	705.26	219.85	1 410.52
			Esomeprazole	1	441.23	0.00	441.23
			Lansoprazole	1	1 439.88	0.00	1 439.88
			Omeprazole	1	704.87	0.00	704.87
			Pantoprazole	2	820.60	154.92	1 641.19
		Lansoprazole	Lansoprazole	3	852.53	400.16	2 557.58
2006	Clarithromycin	Omeprazole	Clarithromycin	1	224.32	0.00	224.32
		Esomeprazole	Esomeprazole	1	686.15	0.00	686.15
		Omeprazole	Rabeprazole	1	610.11	0.00	610.11

Table F2: Combination therapy for the eradication of *H. pylori*, classified as three-drug regimen with four active ingredients, for the five study years.

Year	Active ingredient	Active ingredient	Active ingredient	Active ingredient	Prevalence	Average cost (R) per combination	Std dev $\pm$	Total cost
Clarithromycin/Amoxicillin/PPI								
2001	Amoxicillin	Clarithromycin	Omeprazole	Clarithromycin	1	532.74	0.00	532.74
				Omeprazole	20	1 131.94	165.34	22 638.75
				Pantoprazole	7	1 121.72	177.15	7 852.04
				Rabeprazole	7	1 084.86	74.68	7 594.04
2002	Amoxicillin	Clarithromycin	Omeprazole	Esomeprazole	2	1 031.83	132.74	2 063.66
				Lansoprazole	4	1 226.35	143.29	4 905.38
				Omeprazole	23	1 219.60	217.48	28 050.80
				Rabeprazole	1	1 319.01	0.00	1 319.01
2004	Amoxicillin	Clarithromycin	Omeprazole	Omeprazole	2	1 233.25	365.93	2 466.49
Clarithromycin/Metronidazole/PPI								
2001	Clarithromycin	Metronidazole	Lansoprazole	Lansoprazole	2	1 032.58	932.30	2 065.16
				Pantoprazole	1	1 090.51	0.00	1 090.51
2004	Clarithromycin	Metronidazole	Esomeprazole	Esomeprazole	1	397.07	0.00	397.07
			Esomeprazole	Lansoprazole	1	1 098.90	0.00	1 098.90
2006	Clarithromycin	Metronidazole	Esomeprazole	Lansoprazole	1	636.83	0.00	636.83

Table F3: Combination therapy for the eradication of *H. pylori*, classified as four-drug regimen with five active ingredients, for the five study years.

Year	Active ingredient	Active ingredient	Active ingredient	Active ingredient	Active ingredient	Prevalence	Average cost (R) per combination	Std dev $\pm$	Total cost
Bismuth/Clarithromycin/Tetracycline/PPI									
2004	Bismuth	Metronidazole	Tetracycline	Esomeprazole	Esomeprazole	1	920.59	0	920.59

A LONGITUDINAL ANALYSIS OF THE PRESCRIBING PATTERNS OF ACID REDUCING MEDICINE IN A SECTION OF THE SOUTH AFRICAN PRIVATE SECTOR

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Purpose:

The main objective of this study was to investigate the prescribing patterns and cost of acid reducing medicine with special reference to proton pump inhibitors and histamine-2 receptor antagonists in a section of the private health care sector of South Africa from 2001 to 2006.

Method:

A longitudinal retrospective drug utilisation study was done on acid reducing medicine items claimed through a national medicine claims database for 2001, 2002, 2004, 2005 and 2006. Data were analysed by using the Statistical Analysis System®, SAS 9.1 (SAS for Windows, 9.1, 2005).

Results:

The acid reducing medicine items prescribed decreased from 2.74% during 2001 to 2.50% during 2006 of all medicine items claimed. The same decreasing trend was observed regarding the cost of acid reducing medicine items. The cost percentage decreased from 4.89% (2001) to 3.72% (2006). However, the average cost per medicine item for the acid reducers increased by 5.35% from 2001 (R230.04±176.29) to 2002 (R243.72±184.18) and then decreased by 15.23% from 2002 to 2004. It again decreased with 15.05% from 2004 (R206.19±179.42) to 2006 (R175.70±172.55). The percentage innovator items decreased by 4.50% from 2001 to 2002; increased by 1.01% from 2002 to 2004 and decreased again by 31.06% from 2004 to 2006. The slight increase in the percentage innovator medicine items claimed from 2002 to 2004 may be explained by the introduction of Nexiam® (esomeprazole) into the market in 2002. The total number of generic medicine items claimed contributed between 9.62% (n = R1 788 242.25) in 2001 and 30.75% (n = R3 196 163.34) in 2006 of the total cost of acid reducing medicine items. Proton pump inhibitors represented about half of the acid reducing medicine items prescribed and more than 70% of the total cost of acid reducing medicine items during the study years. The average cost of PPIs revealed a practical significant decrease (d > 0.8) from 2002 (R372.42±156.62) to 2006 (R241.56±177.21). Histamine-2 receptor antagonists (H₂RAs) contributed between 15.00% and 18.26% of all acid reducing medicine items while contributing between 9.68% and 16.85% of the total cost of all acid reducers.

Conclusion:

It can be concluded that the total volume of medicine items and the average price influenced the total cost of medicine items. A decreasing trend was observed from 2001 to 2006 with regard to the percentage contribution of acid reducing medicine to the total number of medicine items claimed and the total cost. This decrease could be explained by a combination of factors namely a change in the medical scheme members and a change in the treatment pattern of acid-related disorders. The decrease in the cost of acid reducers could be the result of the implementation of the new pricing regulations on 2 Augustus 2004. The implications of generic substitution need further investigation with reference to cost and prescribing practices.