A retrospective analysis of the prescribing patterns of isotretinoin

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ABSTRACT

Title: A retrospective analysis of the prescribing patterns of isotretinoin.

Keywords: Isotretinoin, prevalence, age, gender, prescriber, medicinal treatment cost.

Acne is a very common disease affecting approximately 85% of people in some stage of their life (Wolff *et al.*, 2005:2). The systemic drug isotretinoin is the only acne drug which has an influence on all the pathophysiological factors of this highly prevalent disease and is considered as the most effective treatment for acne, although it should be limited to the treatment of severe acne. Isotretinoin prescribing is under the largest risk-minimisation programme (called iPLEDGE) ever implemented for a drug in the United States of America, due to concerns with pregnancies during isotretinoin treatment (Honein *et al.,* 2007:11). In comparison South Africa has no equal managing programme to regulate isotretinoin prescribing and the need to identify certain prescribing patterns is deemed necessary. The general objective of this study was to analyse the prescribing patterns of isotretinoin, including aspects of cost, in a section of the private healthcare sector of South Africa.

A quantitative, retrospective drug utilisation review was performed to evaluate the prescribing patterns and cost of isotretinoin containing products claimed through a pharmacy benefit management organisation, over the study period of 2005 and 2006. Data were analysed by using the Statistical Analysis System, 9.1 (SAS). The information of prescriber, age, gender, and cost of isotretinoin usage were considered and evaluated.

A total number of 6 427 and 6 927 patients claimed 18 589 and 20 232 isotretinoin prescriptions respectively during 2005 and 2006. Isotretinoin total costs contributed to 34.4% (n = R6 810 090) and 36.3% (n = R6 533 241) of the total identified acne medicine costs for 2005 and 2006 respectively. Isotretinoin represented the highest percentage of total costs in relation to any other acne product identified in both study years. Average costs of R314.82 ± 205.92 per prescribed isotretinoin item in 2005 and R277.63 ± 192.63 in 2006 were recorded in comparison to the total database medicine item cost of R95.33 ± 192.21 in 2005 and R95.33 ± 227.99 in 2006.

The generic products of isotretinoin were claimed at a lower ratio (generic vs. innovator product ratio of 1.8:1 in 2005 and 2.2:1 in 2006) in relation to the total database (generic ratio of 3:1 in both years). Dermatologists prescribed 68.2% and 65.7% of isotretinoin

prescriptions and general practitioners 27.5% and 29.7%. General practitioners were more likely to prescribe the generic equivalents of isotretinoin (68.9% in 2005 and 72.1% in 2006) in comparison to dermatologists (59.7% in 2005 and 63.4% in 2006).

The teenage group 12 to 19 years received 48.4% (n = 8 989) and 47.7% (n = 9 656) of isotretinoin prescriptions claimed respectively at an estimated cost of R275 000 and R260 000 per 10 000 beneficiaries in this age group respectively for 2005 and 2006. There were 71 patients identified over both study years in the age group younger than 12 years, in which isotretinoin use is not recommended.

Female patients received 56.2% (n = 10 450) and 57.4% (n = 11 610) of the total number of isotretinoin prescriptions claimed respectively for 2005 and 2006. The average cost per isotretinoin prescription claimed for male patients was higher (R406.36 ± 233.76 and R358.69 ± 218.29 respectively for 2005 and 2006) in relation to female patients (R335.15 ± 209.98 and R296.36 ± 197.74 respectively for 2005 and 2006). The median ages for female and male patients were 21 years and 18 years respectively. The concern, however, was the high number of female patients of child-bearing potential identified (2 892 and 3 201 female patients respectively for 2005 and 2006), claiming their isotretinoin prescriptions.

Systemic isotretinoin occurred alone in 70.8% and 69.3% of prescriptions claimed respectively for 2005 and 2006. Oral contraceptives occurred in combination with isotretinoin in only 8.6% and 9.2% of isotretinoin prescriptions claimed. The contra-indicated use of a systemic tetracycline in combination with systemic isotretinoin occurred in 139 (0.75%) and 130 (0.64%) prescriptions.

It can be concluded that the use of isotretinoin increased. Dermatologists played the major role in prescribing isotretinoin. The number of female isotretinoin users (especially of child-bearing potential) could be a concern, although pregnancy prevalence should be identified in South Africa. It is recommended that further studies be conducted in South Africa regarding the usage and control of isotretinoin, including the extension of regulating programmes, with special reference to age and gender. Effective management of the increasing popularity of this ultimately successful acne treatment is of utmost importance to ensure the effective and safe usage of isotretinoin.

OPSOMMING

Titel: Retrospektiewe ontleding van voorskryfpatrone van isotretinoin.

Sleutelwoorde: Isotretinoin, voorkoms, ouderdom, geslag, voorskrywer, koste van geneesmiddelbehandeling.

Aknee is 'n baie algemene siektetoestand en affekteer ongeveer 85% van alle mense (Wolff *et al.,* 2005:2). Die sistemiese geneesmiddel isotretinoin is die enigste aknee geneesmiddel wat 'n effek het op al die patofisiologiese faktore van hierdie algemene siektetoestand en word beskou as die effektiefste behandeling vir aknee, alhoewel die gebruik beperk moet word tot ernstige aknee. Die voorskryf van isotretinoin in die VSA is onderhewig aan streng regulering, as gevolg van die voorkoms van die teratogene effek by swangerskappe gedurende behandeling met isotretinoin (Honein *et al.,* 2007:11). Suid-Afrika het geen sodanige beheer nie. Gevolglik was dit noodsaaklik om voorskryfpatrone te identifiseer. Die algemene doel van hierdie studie was om die voorskryf patrone van isotretinoin, insluitend die koste, in 'n deel van die privaat gesondheidsektor van Suid-Afrika te ontleed.

'n Kwantitatiewe retrospektiewe navorsingontwerp is uitgevoer om die voorskryfpatrone en koste van isotretinoin produkte wat deur 'n "Pharmacy Benefit Management Organisation" geëis is, oor die jare 2005 en 2006 te ontleed. Die analise van die data is met behulp van SAS (Statistical Analysis System, 9.1) gedoen. Die inligting oor die voorskrywer, ouderdom, geslag en koste van isotretinoin gebruik is beskou en geëvalueer.

Vir 'n totaal van 6 427 en 6 927 pasiënte is 18 589 en 20 232 isotretinoin voorskrifte onderskeidelik in 2005 en 2006 geëis. Die totale koste wat isotretinoin bygedra het tot die totale aantal geïdentifiseerde aknee-middelkoste vir 2005 en 2006 is 34.4% (n = R6 810 090) en 36.3% (n = R6 533 241) onderskeidelik. Isotretinoin verteenwoordig die hoogste persentasie van die totale koste in vergelyking met enige van die ander geïdentifiseerde aknee-produkte in beide studiejare. 'n Gemiddelde koste van R314.82 ± 205.92 per voorgeskryfde isotretinoin item in 2005 en R277.63 ± 192.63 in 2006 is geïdentifiseer in vergelyking met die gemiddelde itemkoste op die databasis van R95.33 ± 192.21 in 2005 en R95.33 ± 227.99 in 2006.

Die generiese isotretinoin produkte is geëis teen 'n laer verhouding (generies vs. oorspronklike produk verhouding van 1.8:1 in 2005 en 2.2:1 in 2006) in vergelyking met die

totale databasis (generiese verhouding van 3:1 in beide jare). Dermatoloë was verantwoordelik vir 68.2% en 65.7% van alle isotretinoin-voorskrifte teenoor algemene praktisyns met 27.5% en 29.7% voorskrifte onderskeidelik vir 2005 en 2006. Algemene praktisyns is meer geneig om generiese produkte van isotretinoin voor te skryf (68.9% in 2005 en 72.1% in 2006) in vergelyking met dermatoloë (59.7% in 2005 en 63.4% in 2006).

Vir die tienergroep van 12 tot 19 jaar is 48.4% (n = 8 989) en 47.7% (n = 9 6560) van isotretinoin voorskrifte ge-eis vir 2005 en 2006 onderskeidelik en wel teen 'n beraamde koste van R275 000 en R260 000 per 10 000 begunstigdes in hierdie ouderdomgroep vir 2005 en 2006 onderskeidelik. Ten spyte daarvan dat isotretinoin nie vir die ouderdomgroep 12 jaar en jonger aanbeveel word nie, is dit wel aan 71 pasiënte gedurende 2005-2006 voorgeskryf.

Vroulike pasiënte het 56.2% (n = 10 450) en 57.4% (n = 11 610) van die totale aantal isotretinoin voorskrifte wat geeïs is, ontvang vir 2005 en 2006 onderskeidelik. Die gemiddelde koste per isotretinoin voorskrif vir manlike pasiënte was hoër (R406.36±233.76 en R358.69 ± 218.29 onderskeidelik vir 2005 en 2006) in vergelyking met vroulike pasiënte (R335.15 ± 209.98 en R296.26 ± 197.74 onderskeidelik vir 2005 en 2006). Die mediaan ouderdom vir vroulike en manlike pasiënte was 21 jaar en 18 jaar onderskeidelik. Kommerwekkend was egter die hoë aantal vroulike pasiënte in hul vrugbaarheidsjare wat geïdentifiseer is (2 892 en 3 201 vroulike pasiënte vir 2005 en 2006 onderskeidelik) deur wie isotretinoin ge-eis is.

Sistemiese isotretinoin is as enkelgeneesmiddel in 70.8% (2005) en 69.3% (2006) van isotretinoin voorskrifte geeïs. Volgens die eise kom orale kontraseptiva in kombinasie met isotretinoin slegs in 8.6% en 9.2% van isotretinoin-voorskrifte voor. Die gebruik van orale tetrasikliene saam met sistemiese isotretinoin, wat teenaangedui is, het op 139 (0.75%) en 130 (0.64%) van die voorskrifte voorgekom.

Samevattend blyk dit dat die gebruik van isotretinoin toegeneem het. Dermatoloë is die vernaamste voorskrywers van isotretinoin. Die aantal vroulike pasiënte wat isotretinoin gebruik (veral in hul vrugbaarheidsjare) dui op 'n moontlike probleem, alhoewel swangerskap voorkoms tydens gebruik van isotretinoin in Suid-Afrikaanse konteks nog geïdentifiseer moet word. Daar word aanbeveel dat verdere studies gedoen word met betrekking tot die gebruik van en die moontlike kontrole oor die voorskryf, insluitend die uitbreiding van die regulerings programme, met 'n spesiale fokus op ouderdom en geslag in Suid-Afrika. Effektiewe bestuur van die toenemende populariteit van die uiters suksesvolle aknee-behandeling is van kardinale belang om te verseker dat isotretinoin effektief en veilig gebruik word.

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First Runner-up Winner – Young Scientist Competition 2008.

INDEX

LIST OF FIGURES

LIST OF TABLES

A RETROSPECTIVE ANALYSIS OF THE PRESCRIBING PATTERNS OF ISOTRETINOIN

CHAPTER 1

INTRODUCTION

Acne is a very common disease and effects large numbers of people all over the world. Isotretinoin is the miracle drug saving countless of people from the severe cases of this embarrassing disease called acne. This dissertation will focus on the prescribing patterns and usage of isotretinoin, mainly for acne, according to a medicine claims database in the private healthcare sector of South Africa.

1.1 PROBLEM STATEMENT

A person's skin is a very obvious part of his or her body, especially the face, making acne a disease about which people are sensitive. Having acne is stressful and it negatively affects one's quality of life (Gupta, 1998:451; Jobanputra & Bachmann, 2000:826). In the previous decade acne was the most common dermatological condition, reportedly affecting 85% of teenage boys and 80% of teenage girls (Simpson, 1994:108-113). In 1996 acne was also the most common reason why persons aged 15 to 45 visited a dermatologist in the USA (Stem, 1996:776-780). Increased incidence is seen in 14 to 17-year-old females and 16 to 19-year-old males, and it is more frequent and more severe in males (Cunliffe, 1998:1927-1984). According to Suganthi (2005:224-228) there has been a shift towards non-antibiotic treatment in acne management since 1990 to 2002, with a significant increase in topical retinoids and oral isotretinoin during this period.

The systemic drug isotretinoin is the only acne drug which has an influence on all the pathophysiological factors of this highly prevalent disease and is considered as the most effective treatment for severe acne (Gollnick *et al.,* 2003:S26; Sinclair & Jordaan, 2005:889). The management of acne has been radically altered by the introduction of isotretinoin in 1982 (became available in South Africa in 1984), since then isotretinoin has become well recognised as the most successful therapy for acne vulgaris (Koran, 2004:505; Presbury, 1997:1410). Between 1992 and 2000, there has been a 2.5 fold (250%) increase in the number of dispensed prescriptions for isotretinoin in the United States of America (Retail pharmacies dispensed 19.8 million outpatient prescriptions for isotretinoin in 1982 through to

2000) emphasising the increased importance of isotretinoin (Wysowski *et al.*, 2002:505). This increase occurred before the generic products of systemic isotretinoin were introduced in 2002 (Koren *et al.,* 2004:1567). Wysowski *et al.* (2002:505) also revealed an increased proportion of 31% to 49% in the usage of isotretinoin in mild and moderate acne (although isotretinoin is only indicated for severe acne). They also indicated that the sex distribution of patients was nearly even, and 63% of male patients to whom isotretinoin had been prescribed were 15 to 19 years old, whereas 51% of female patients were 15 to 24 years old.

Wessels *et al.*, (1999:784) did a meta-analysis on the success rate of isotretinoin and calculated a high success rate, between 84.2% and 86.7%, at an average treatment period of 17.9 weeks (4 months), with dosages of isotretinoin ranging from 0.33 to 1mg/kg/day, at a low relapse rate of 21.5%. In the year 1999, after the cost-effectiveness study had been done by Wessels *et al.*, (1999:785) the annual pharmacotherapy expense per patient on isotretinoin was R6 140, indicating that this is a very expensive treatment and furthermore the treatment of acne represented a significant burden to funders, estimated at R7.2 million per 100 000 beneficiaries.

However, this drug causes numerous side-effects. The less serious side-effects, but most common, were the mucocutaneous side-effects presenting as dryness of the eyes, lips, mouth, cheilitis and other epidermal surfaces (Gibbon *et al.*, 2005:194). These effects are dose dependent (due to the sebum suppression effect of the drug), tolerable, and treatable (McLane, 2001:188). This implies that there are probably more costs related to the treatment of acne with isotretinoin. The more serious side-effects include depression, liver and blood effects, and teratogenicity (the biggest concern). These concerns, especially the teratogenic effect, led to various forms of managing programmes, implemented over the last few decades in some parts of the world, to address the issues of systemic isotretinoin. The most recent managing programme in the USA is called the IPLEDGE (started on, 1 March 2006), which contains numerous registry rules before isotretinoin can be prescribed to a female patient (especially female patients of child-bearing age). These registry rules must be followed by the manufacturer, prescriber, pharmacist and especially the patient (FDA, 2005). There is no specific managing programme in South Africa although there has been a recent acne guideline update that was done by Sinclair and Jordaan (2005:889), giving the recommended guidelines that should be followed when isotretinoin is prescribed. Because of the teratogenic effect of the drug, monthly negative pregnancy tests are recommended in South Africa but are compulsory in the USA under their managing programme (Sinclair & Jordaan, 2005:889; FDA, 2005). Consensus has not been reached on the issue of depression and suicide resulting from the use of isotretinoin (Hersom *et al.*, 2003:430-431; Jick, 2000:1231). Isotretinoin has been part of controversy since it first entered the market (in

1982) and to ensure that this highly effective drug stays on the market it is important to manage the drug correctly and to emphasise the successful and safe usage of isotretinoin.

From the foregoing discussion, it is apparent that research on the prescribing patterns and usage of isotretinoin in South Africa is imperative. The effect that isotretinoin has on the private health care sector in South Africa should also be monitored. The aim of this study was, accordingly, to perform a retrospective drug utilisation study of the prescribing patterns of isotretinoin.

The research questions for the study were:

- How can acne and isotretinoin usage be defined?
- Does the database indicate an increased frequency in the prescribing of isotretinoin in this section of the private heath care over the two study years, 2005 to 2006?
- How prevalent is isotretinoin treatment in relation to other acne treatments claimed through the database?
- What is the treatment cost of isotretinoin prescriptions and what effect does it have on the private health care sector?
- Are the innovator isotretinoin products still preferred to the generic products and what is the difference in cost between the innovator and generic products?
- Who are the major prescribers of isotretinion and do different prescribers differ in their prescribing patterns?
- Are there any differences in isotretinoin usage according to different age groups?
- What are the gender differences in isotretinoin usage and are there reasons for concern?
- How does isotretinoin compare with other acne medications and medicine products overall according to cost and/or usage?
- What medicine combinations occur on isotretinoin prescriptions and are there reasons for concern?

1.2 RESEARCH OBJECTIVES

This research project includes general as well as specific objectives

1.2.1 General objective

The general objective of this study was to review the prescribing patterns and cost of isotretinoin according to a medicine claims database for the period 2005 to 2006 in a section of the South African private health care sector.

1.2.2 Specific objectives

The specific objectives include the following:

1.2.2.1 Literature objectives:

The literature study served the purpose of reviewing the necessary information relating to the background needed to understand acne and the treatment thereof, with special reference to isotretinoin. The specific research objectives of the literature study were as follows:

- To present a brief overview of the anatomy of the skin, with reference to the pilosebaceous unit.
- To review acne as a disease and the treatments available.
- To present an overview (including indications, dosages, adverse effects and interactions) of isotretinoin treatment through available literature.
- To investigate different aspects (including age, gender and prescribers) of isotretinoin treatment through available literature.
- To mention briefly what managed health care, including drug utilisation review, pharmacoepidemiology and pharmacoeconomics, consist of.

1.2.2.2 Empirical objectives:

The empirical study served the purpose of evaluating the available information through a medicine claims database to reveal some prescribing patterns of isotretinoin in a section of the South African private health care sector. The specific research objectives of the empirical study were as follows:

- To determine the prescribing patterns including aspects of cost of isotretinoin products, with comparisons to acne products and the total claimed medicine items in a section of the private healthcare sector of South Africa.
- To determine the cost and prevalence difference between the innovator and the generic isotretinoin products.
- To identify the differences in prescribing patterns of isotretinoin between the major medical prescribers of isotretinoin.
- To identify age group differences in the prescribing patterns of isotretinoin.
- To determine and identify the difference in the prescribing patterns of isotretinoin in the different genders.
- To identify combination therapy with isotretinoin products and determine any possible concerns.

1.3 RESEARCH METHOD

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

1.3.1 Phase one: Literature review

The literature review can be divided into two parts. The first part contains a discussion of the skin and acne, together with the treatment thereof especially with isotretinoin. In this discussion an overview of the definitions, aetiology, clinical findings (signs and symptoms), pathogeneses, complications, effects and side-effects of acne and isotretinoin treatment is presented. The pharmacological overview includes the mechanism of action, dosage, tolerability and drug interactions of isotretinoin.

In the second part the focus is mainly on isotretinoin usage and what is available in the literature regarding isotretinoin usage and management. This section also includes a brief look at managed health care concepts relevant to this study, including drug utilisation. These aspects are defined and discussed with reference to the usage patterns of isotretinoin.

1.3.2 Phase two: Empirical investigation

This empirical investigation consists of four phases (discussed in chapter 3), namely:

- The selection of measuring instruments
- Data analysis
- The report and discussion of the results of the empirical investigation
- Conclusions and recommendations based on the results of the empirical investigations.

A retrospective drug utilisation study was done on data provided by a pharmacy benefit management company (medicine claims database) over the time period of 2005 and 2006. The medicine claims database included approximately 34% of the total number of beneficiaries in the private heath care sector of South Africa. The Statistical Analysis system (SAS for Windows, 9.1, 2005) was used to conduct comparative analyses.

1.4 ETHICAL APPROVAL

Within the medicine claims database the individual patients and prescribers could not be identified and the study allowed for them to remain anonymous. Ethical approval was obtained at the North-West University (NWU-0046-08-S5).

1.5 DIVISION OF CHAPTERS

Chapter 1: Introduction

Chapter 2: Isotretinoin and acne overview

Chapter 3: Empirical investigation

Chapter 4: Results and discussion

Chapter 5: Conclusions, recommendations and limitations

1.6 CHAPTER SUMMARY

This chapter consists of an introduction. The basic plan of how the study was conducted has been outlined. Firstly the relevant information gained by the literature study is discussed under chapter two. A discussion of the methods, results and other aspects of the empirical study follows in chapters three to five. The arrangement of chapters has also been indicated. In the next chapter the aspects of acne and isotretinoin are being discussed.

CHAPTER 2

ACNE AND ISOTRETINOIN

This chapter consists of a description of the skin, acne and focuses on the treatment of acne with isotretinoin. The aspects of isotretinoin usage available in the literature will be discussed together with heath care concepts relevant to this study.

2.1 SKIN ANATOMY

The skin is the largest organ of the human body and is made up of multiple layers of epithelial tissues that guard underlying muscles and organs. As it interfaces with the surroundings, it plays the most important role in protecting the body against pathogens (Swanson, 2008). The skin is only about 2 mm thick and on average, an adult has about two square meters of skin, which weighs about 2.7 kg. It is also very involved in maintaining the proper temperature for the body to function, gathering sensory information from the environment and plays an active role in the immune system. The skin is also the organ that is most visible to the people around us, especially the facial area. For these reasons it is important to keep a healthy skin (Swanson, 2008; Kamel, 2008). Understanding how the skin can function in these many ways starts with understanding the structure of the 3 layers of skin, *i.e.* the epidermis, dermis, and subcutaneous tissue (hypodermis) (Fig. 2.1) (Butler, 2008; Yung, 2008).

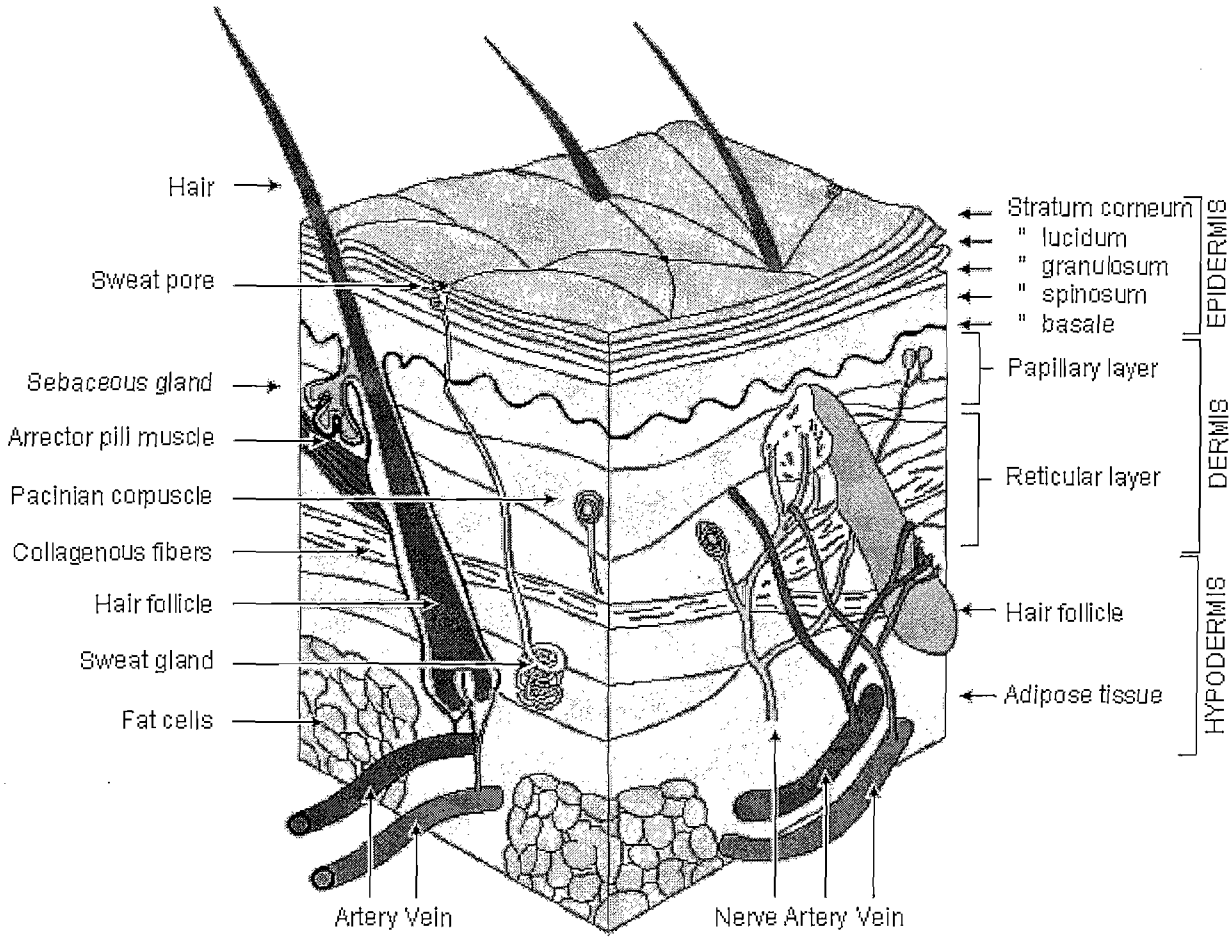

Figure 2.1: Skin structure (Butler, 2008)

2.1.1 Epidermis

The epidermis is the outermost layer of the skin (Fig. 2.1), the final boundary between body and environment. The epidermis contains no blood vessels and depends entirely on the dermis for nutrients and the removal of waste (Dermatology channel, 2007; Revis & Seagel, 2003).

This top layer is only 0.1 to 1.5 mm thick and made up of five smaller layers. From bottom to top, the layers are named as follows (Fig. 2.1):

- *stratum basale*
- *stratum spinosum*
- *stratum granulosum*

- *stratum lucidum*
- *stratum corneum* (Yung, 2008)

The bottom layer, the *stratum basale*, has cells that are shaped like columns. In this layer the cells divide and push already formed cells into higher layers. As the cells move into the higher layers, they flatten and eventually die (Swanson, 2008). The process from cell division to shedding takes approximately 28 days in normal skin (Powell, 2006:1).

The top layer of the epidermis, the *stratum corneum* (also known as the horny layer), is made up of dead, flat skin cells that shed about every 2 weeks (Yung, 2008). This top layer is an effective barrier to most organisms, chemicals and fluids, although it is permeable to some substances (hence topical treatments). It also protects against uncontrolled loss of fluid from the body (Powell, 2006:3).

There are three types of specialised cells in the epidermis, namely

- the melanocyte (Fig. 2.1) produces pigment (melanin), a protection against ultraviolet radiation;
- the Langerhans' cell (Fig. 2.1) is the frontline defence of the immune system in the skin; and
- the Merkel's cell's (Fig. 2.1) exact role or function is not well understood, it is thought that they may be transducers for fine touch (Yung, 2008; Powall, 2006:1).

2.1.2 Dermis

The dermis varies in thickness depending on the location of the skin and ranges from 0.3 mm on the eyelid to 3.0 mm on the back (About, 2007). It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands and blood vessels (Fig. 2.1) (Dermatology channel, 2007).

This second layer of skin consists of various connective tissues throughout – not in layers. The types of tissue are

- collagen; and
- elastin (Yung, 2008)

These types of tissue provide strength, extensibility (the ability to be stretched), and elasticity (the ability to return to its original form) to the dermis structure (Cliffnotes, 2008).

The two layers of the dermis are the papillary and reticular layers (Fig. 2.1):

- The upper papillary layer contains a thin arrangement of collagen tissue. This outer layer forms finger-like projections called dermal papillae that protrude into the epidermis. In the hands and feet, the dermal papillae generate epidermal ridges (swear from the epidermal ridges leaves fingerprints). This layer has two important functions, the first being to support the epidermis with vital nutrients and secondly to provide a network for thermoregulation (Swanson, 2008; Dermatology channel, 2007).

- The lower reticular layer is thicker and made of thick collagen tissue that is arranged parallel to the surface of the skin, giving the skin its overall strength and elasticity. It also houses other important epithelial-derived structures such as glands and hair follicles (Swanson, 2008; Cliffnotes, 2008).

The most important function of the dermis for this study is that it contains the pilosebaceous unit with the sebaceous gland.

2.1.3 Subcutaneous tissue

The subcutaneous tissue (also known as the hypodermis) is a layer of fat and connective tissue that houses larger blood vessels and nerves (Fig. 2.1). This layer is also important in the regulation of temperature, fastening the skin to the underlying surface and absorbing shocks from impacts to the skin. The size of this layer varies throughout the body and from person to person (Yung, 2008; Cliffnotes, 2008).

The skin is a complicated structure with many functions and if any of the structures in the skin are not working properly, a rash or abnormal sensation is the result most of the time. The entire specialty of dermatology is devoted to understanding the skin and its functions and to developing cures for skin irregularities.

2.2 PILOSEBACEOUS UNIT

Pilosebaceous unit consists of the hair follicle, hair shaft and sebaceous gland (Fig.2.2) (Singh *et al.*, 2000:269). The most important area of the pilosebaceous unit for this study is the sebaceous gland.

2.2.1 Sebaceous gland

The human sebaceous glands are found throughout the skin except for the palms of the hands and the soles of the feet and are associated with a hair follicle to form the pilosebaceous unit; it is a slightly mysterious gland whose functions are still not fully understood (Downie *et al.*, 2004:291; Thiboutot, 2004:1). The number of sebaceous glands remains approximately constant throughout life, whereas their size tends to increase with age (Fenske & Lober, 1986:571).

These glands are largest and most concentrated in the face and scalp area, the site of origin for most cases of acne development. The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils as seen in table 2.1 (eMedicine, 2007). Table 2.1 indicates the big difference between sebum secreted by the sebaceous glands and the normal epidermal surface lipids (Thiboutot, 2004:3). These differences may indicate why *Propionibacterium acnes* grow rapidly in sebum.

Table 2.1: Composition of Human Sebum vs. Epidermal Lipids (Thiboutot, 2004:3)

Lipid	Sebum Weight (%)	Epidermal surface lipid Weight (%)
Triglycerides, diglycerides and free fatty acids	57	65
Wax esters	26	-
Squalene	12	-
Cholesterol	2	20

Synthesis and discharge of sebum contained in sebaceous cells take more than one week and the turnover of sebaceous glands is slower in older than in young adults (Plewig &

Kligman, 1978:314). The function of sebum is not fully known, but it is thought to keep the skin moist, flexible, to protect against friction and collectively works with other natural oils to form a barrier known as the hydro-lipid system which keeps foreign substances out of our bodies and keeps water inside the body, making it water-resistant (Quick Acne Remedy, 2007; Thiboutot, 2004:1).

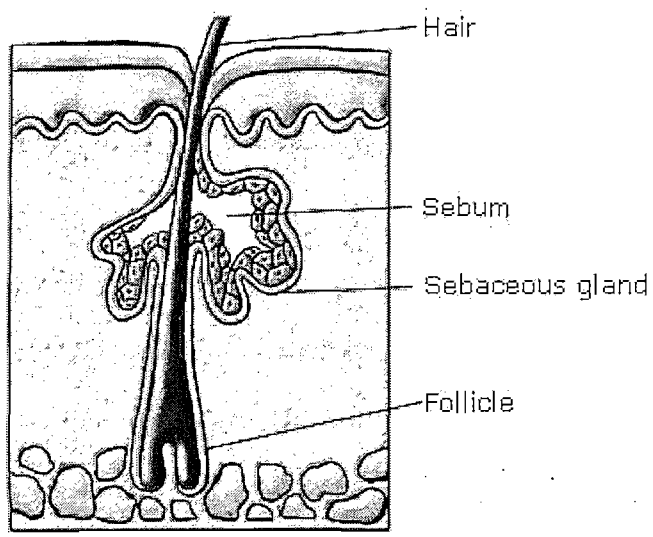

Figure 2.2: Sebaceous gland (Pharmacy 2 u, 2007)

Although everything about the sebaceous gland is not fully known, it is known as the area in which acne develops (Thiboutot, 2004:1).

2.2.1.1 Sebaceous gland function in acne

The sebaceous gland functions, which are possibly involved in the development of acne, are the following (Zouboulis, 2004:361):

- Production of sebum
- Regulation of cutaneous steroidogenesis
- Regulation of local androgen synthesis
- Interaction with neuropeptides
- *Synthesis of specific lipids with antimicrobial activity*

- Exhibition of pro- and anti-inflammatory properties

By taking a closer look at these functions of the sebaceous gland a clearer view of what role some of these functions play in the development of acne could be identified.

2.2.1.1.1 Sebum production

Sebaceous glands on the back, forehead and chin are larger and more numerous than elsewhere on the body and there could be up to 400-900 glands per square centimetre, which explains why more sebum is produced in these areas and a reason why these areas are more susceptible to acne (Oakley, 2007).

Sebum production is under the control of sex hormones (androgens) and the most active androgens are testosterone, 5-testosterone (DHT) and 5-androstene-317diol. These hormones and others are produced by the sex glands (ovary in females, testis in males) and the adrenal gland. These glands are in turn under the influence of the pituitary gland, located in the brain (Oakley, 2007).

An increase in sebum excretion occurs a few hours after birth and peaks during the first week and then slowly decline over the next few months (Henderson *et al.,* 2000:111). Sebaceous secretion is low in children and begins to increase in mid- to late childhood under the influence of androgens and this rise continues until late teens, after which no further significant change takes place until late in life when it decreases gradually (a noticeable decrease happens after menopause in women) (Pochi *et al.,* 1979:108).

Acne cannot occur without sebum, which serves as a nutrient source for *Propionibacterium acnes,* and only a few therapeutic agents apart from 13-cis retinoic acid (isotretinoin) and systemic anti-androgens (for use in women only) are effective inhibitors of sebum production (Thiboutot, 2004:1). Normal sebum secretion does not cause acne, but when the secretion is blocked the end result is usually acne.

2.2.1.1.2 Hormonal Control of the Sebaceous Gland

In the human body, the sebaceous gland is large at birth and remains so during the first few weeks after birth with high sebum levels on the forehead just as high as in their adulthood; this is presumably because of the influence of maternal androgens (Henderson *et al.,* 2000:110). However, the effect of maternal androgens soon wears off and glands then

involute and remain quiescent until puberty when the androgen surge causes glands to enlarge and sebum output to increase more than fivefold (Pochi *et al.,* 1979:108).

The most likely important end-organ androgen for sebaceous gland function is dihydrotestosterone, which is converted from testosterone by 5α-reductase (Holland *et al.,* 1998:102). Overall levels of 5α-reductase have been shown to be higher in the sebaceous gland of patients with acne than those without acne (Sansone & Reiser, 1971:370), although the cellular and molecular mechanisms by which androgens exert their influence on the sebaceous gland have not been fully elucidated (Thiboutot, 2004:4). The essential role for androgens in stimulating sebum production is seen through the following clinical evidence:

- The development of early acne in the pre-pubertal period has been associated with elevated serum levels of dehydroepiandrosterone sulfate (DHEAS), a precursor for testosterone (Stewart *et al.,* 1992:1345).

- Androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne (Imperato-McGinley *et al.,* 1993:526).

- Androgen-producing tumours of the ovary or adrenal gland are often associated with the development of acne (Thiboutot, 2004:419).

- Systemic administration of testosterone and DHEAS increases the size and secretion of sebaceous glands (Pochi & Strauss, 1969:32).

- Severe acne is often associated with elevated serum androgen levels (Marynick *et al.,* 1983:981).

Even when exogenous testosterone is applied on the forehead it showed an increase in sebum secretion rates. This demonstrates that sebaceous glands are stimulated by androgens to varying degrees and support the theory of an end-organ response in acne (Holland *et al.,* 1998:102).

Very little is known about the role of estrogens in modulating sebum production although estrogens may act by several mechanisms, including (1) directly opposing the effect of androgens locally within the sebaceous gland, (2) inhibiting the production of androgens by gonadal tissue via a negative feedback loop on pituitary gonadotrophin release, and (3) regulating genes that negatively influence sebaceous gland growth or lipid production (Thiboutot, 2004:421).

All of these points prove the important role hormonal concepts play in the sebaceous gland functions and of course acne. But still nothing is totally clear about the roles of different hormones and the effect that they have on the skin, especially acne.

2.3 ACNE

Acne vulgaris is an easily recognisable dermatologic disease which is very common and is seen in nearly 100% of individuals at some time during their lives. Small, non-inflamed acne lesions may not be more than a slight nuisance to patients, but in individuals with more severe inflammatory nodular acne associated with pain, social embarrassment, and both physical and psychological scarring the effect of this acne can be life-altering. Fortunately, our understanding of the pathogenesis of acne has progressed and our therapeutic armamentarium has greatly expanded in the last twenty-five years (Harper, 2004:S36).

The most updated definition identified for acne by Strauss *et al.* (2007:652), defined acne as a chronic inflammatory dermatosis which is notable for open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules.

2.3.1 Epidemiology

Acne vulgaris (more commonly referred to simply as acne) is a very common disorder among young people, affecting approximately 85% of people, with an onset at puberty – ages 10 to 17 years in females and 14 to 19 in males. However, in many cases it may first appear at a later age of 25 years or older. Acne is usually more severe in males than in females. (Wolff *et al.,* 2005:2)

In an article published in the US Pharmacist (Pal, 1997:4) it was suggested that 17 million persons in the US suffer from *acne vulgaris*, with a projected age distribution of

85% in the age group 12-24yrs,

8% in the age group 25-34yrs,

3% in the age group 35-44yrs.

There is usually a decrease in the prevalence of acne with an increase in age.

Dermatologists see more patients for acne-related disorders than for any other skin condition, emphasising the extended effect acne has on the population (Pal, 1997:4).

The name acne comes from the Greek word 'acme', which means the prime of life (peak), because it is a common problem in younger years (BBC, 2007).

2.3.2 Pathogenesis

The clinical definition for *Acne vulgaris* is the inflammation of the pilosebaceous units of certain body areas (face and trunk, rarely buttocks) that occurs most frequently in adolescence and manifests itself as comedones (non-inflammatory lesions), papulopustules (inflammatory lesions), or nodules and cysts (Wolff *et al.,* 2005:2).

The most notable pathophysiologic factors that influence the development of acne (Fig. 2.3) are the following:

- Production of androgens in the body
- Sebaceous gland hyperplasia with seborrhea
- Altered follicular growth and differentiation
- *Propionibacterium acnes* colonisation of the follicle
- Inflammation and immune response (Gollnick *et al.,* 2003:S2)

Of these, altered follicular growth and differentiation and sebaceous hyperplasia are the most important, because they combine to induce the microcomedo – the primary lesion of acne (Fig. 2.4) (Gollnick *et al.,* 2003:S2). This lesion is characterised by follicular plugging with no inflammation or the bacteria, *P. acnes,* are observed at this stage. The lesion is also not visible to the naked eye but histological analysis shows hyperkeratosis of the intrafollicular sebaceous ducts and dilatation of the sebaceous glands. In the acne-prone patient, about 30% of facial follicles will be in this state at any given time (Sinclair & Jordaan, 2005:884). The stimulus for microcomedo formation is still unknown, although leading hypotheses implicate androgen hormones, alterations in follicular linoleic acid levels and the inflammatory cytokine interleukin-1α may be the reason (Harper, 2004:36). The microcomedo can evolve into either a non-inflammatory comedo or become inflamed and present as a papule, pustule, or nodule (Fig. 2.5) (Gollnick *et al.,* 2003:S2).

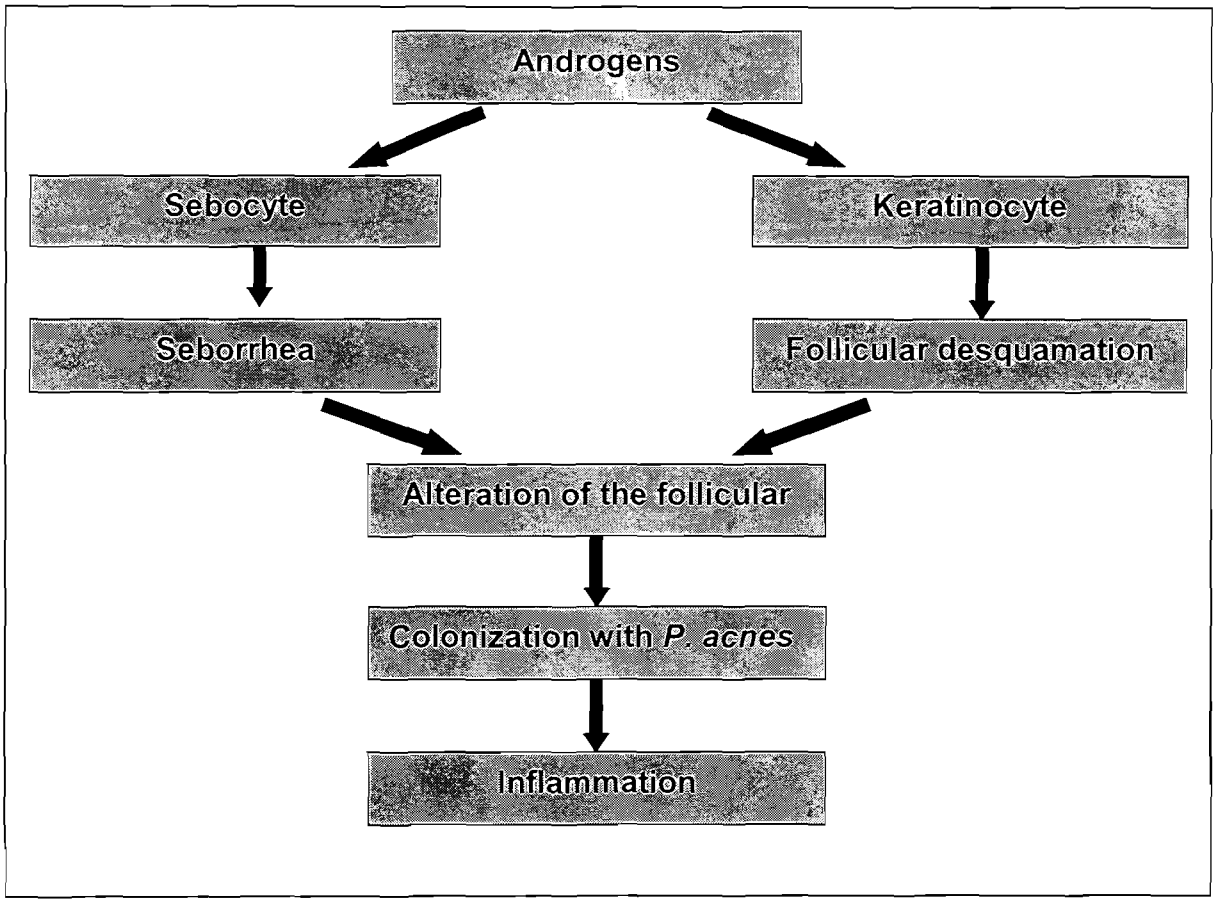

Figure 2.3: Pathogenesis of acne (Plewig & Kligman, 2000)

P. acnes, the harmless member of the resident cutaneous flora, proliferates in the environment of the microcomedo and this bacterium is present in increased numbers in persons who have acne (Leyden, 2001:142). Much of the inflammation that eventually occurs arises from the action of enzymes produced by the bacteria. These enzymes hydrolyse sebum into free fatty acids, which stimulate the inflammatory process. Chemotactic factors are released by this reaction, attracting neutrophils. As the follicular wall becomes inflamed, an erythematous papule appears on the skin surface. With increased sebum production, obstruction and bacterial colonisation, the follicular unit ruptures then spilling its contents into the dermis. The inflow of neutrophils causes the formation of pustules (Fig. 2.5). Continuation of severe inflammation leads to formation of nodules and subsequent cysts (Johnson & Nunley, 2000:1823).

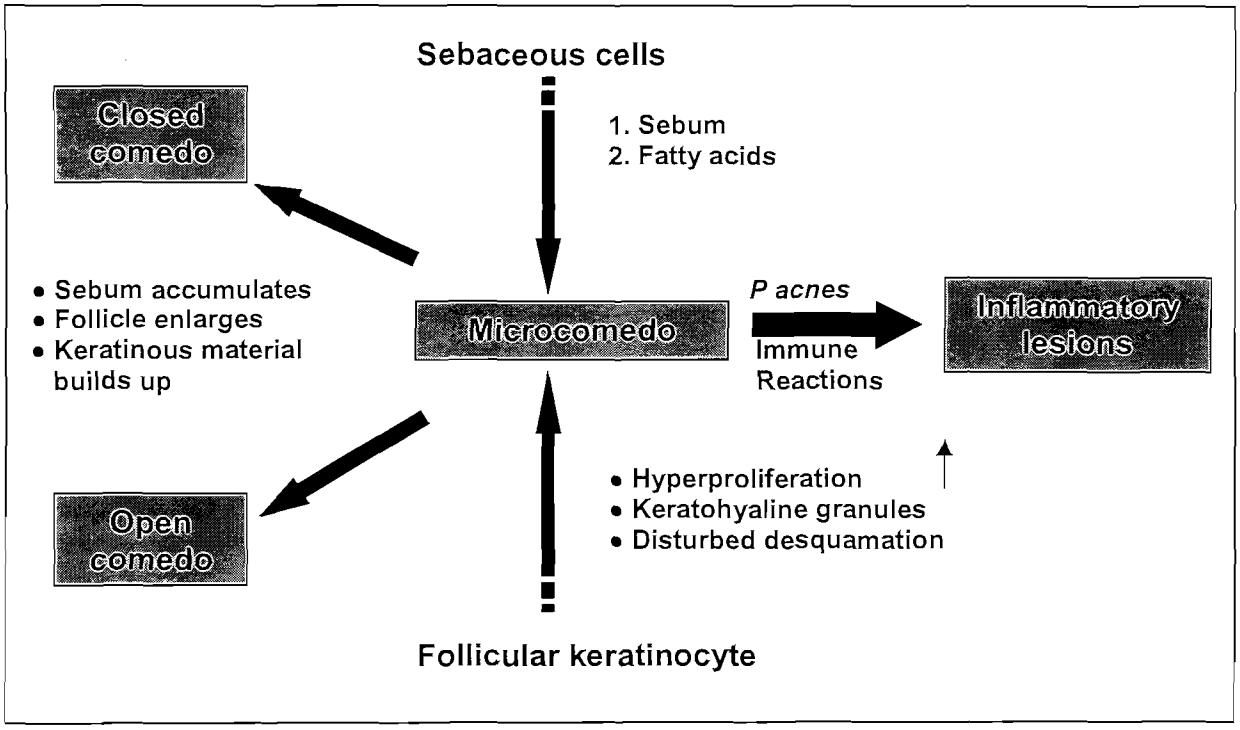

Figure 2.4: Lesion progression in acne (Gollnick *et al.*, 2003:3)

Androgens play an important role in the pathogenesis of acne, but still most patients with acne have normal hormone levels. Presently, there is little evidence from peer reviewed literature indicating that routine endocrinologic testing has clinical value in the evaluation of patients with acne (Strauss *et al.*, 2007:653). Although sebum production increases during adolescence (particularly in boys, because of androgen stimulation), the increase of sebum alone does not cause acne (Johnson & Nunley, 2000:1823).

It is clear to us that acne is a collection of related disorders and that diversity exists between different individuals and populations (Holland & Jeremy, 2005:82).

The effect of diet in the pathogenesis of acne is still not clearly known with the last specific diet-acne trial published more than 30 years ago, stating that there is no correlation. In the years that followed, great strides have been made in understanding how diet influences long-term health and well-being. Unfortunately, appreciation of this information has generally gone unnoticed in the dermatology community, as witnessed by the 30-plus year vacuum since the last dietary intervention in acne patients (Cordain, 2005:89).

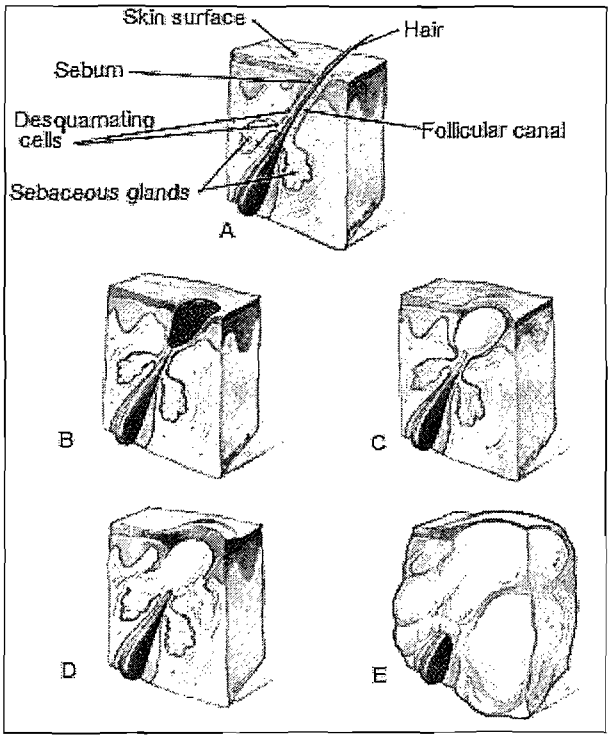

Figure 2.5: Stages of acne. *(A)* Normal follicle; *(B)* open comedo (blackhead); *(C)* closed comedo (whitehead); *(D)* papule; *(E)* pustule (Johnson & Nunley, 2000:1824).

A recent study was done by Mann and Smith (2007:4) which showed that by eating a healthy, well-balanced diet with minimum amounts of processed foods helped improve acne symptoms and reduce the psychological impact of acne. The improvement in acne has also been associated with changes in hormones, providing further support for the dietary connection. These results provide evidence that diet may play a role in acne. Although a substantial body of literature now exists that directly implicates diet as the most likely environmental factor underlying the development of acne, the confirmation of the diet-acne hypothesis will require numerous well controlled dietary interventions examining multiple nutritional factors (Cordain, 2005:89).

Much remains unknown in our understanding of the pathogenesis of acne. Why do some persons develop acne and others do not despite similar serum hormone levels and similar *P. acnes* counts? What determines the severity of acne in a given patient? Is acne primarily an inflammatory dermatosis? What role does diet play in acne? Much progress has been made in the study of acne, but many questions remain. Perhaps the most important question is, how do we treat our patients with acne more effectively and safely than we are doing now? The answer to this question lies in the development of a deeper understanding of the pathogenesis of *acne vulgaris* (Harper & Thiboutot, 2003:1).

2.3.3 Acne grading

The necessity to classify and grade *acne vulgaris* according to severity plays a very important role in decision making when treatment is planned. However, grading can be very problematic and highly subjective, especially when clinicians also use the number of different skin lesions to determine severity (Sinclair & Jordaan, 2005:885). There is still a need for better acne grading systems that could be used all over the world and at present there is no consensus on a best grading or classification system for acne (Strauss *et al.*, 2007:652; Witkowski & Parish, 2004:396). Currently there are many different acne grading and classification systems and a quick review of some of these systems follows below:

Acne is classified as mild, moderate, or severe (Healy & Simpson, 1994:831).

- Mild acne is defined as non-inflammatory lesions (comedones), a few inflammatory (papulopustular) lesions, or both.
- Moderate acne is defined as more inflammatory lesions, occasional nodules, or both, and mild scarring.
- Severe acne is defined as widespread inflammatory lesions, nodules, or both, and scarring; moderate acne that has not settled within 6 months of treatment; or acne of any "severity" with serious psychological upset. (BMJ Clinical Evidence, 2007)

In the case of grading acne the simplest way is based on the predominant type of lesion present on the skin, regardless of the number. This makes therapeutic sense if one assumes that, for example, one comedo present on the face will respond as well to treatment as several comedones would. That is why Sinclair and Jordaan (2005:885) suggested that grading should always be done according to the most severe lesions present and treatment then be decided accordingly.

One can therefore grade acne as follows, indicated in table 2.2 (this grading system is also used in South Africa as shown in the article "Acne Guideline 2005 Update" by Sinclair & Jordaan):

Table 2.2: Acne grading system (Sinclair & Jordaan, 2005:885).

Grade 1	Comedones only (whiteheads or blackheads)
Grade 2	Inflammatory papules present in addition to the comedones
Grade 3	Pustules present in addition to any of the above
Grade 4	Nodules, cysts, conglobate lesions or ulcers present in addition to any of the above

This is a very simple grading system, but there are more complicated grading systems which rely heavily on the use of photographs or diagrams. In such systems the clinical appearance of the patient is decided on according to correspondence with a particular photograph. This system is often difficult to reproduce, highly subjective and does not always reflect the exact pathology present and therefore is not reliable in indicating the exact treatment required for the particular case (Sinclair & Jordaan, 2005:885).

In the process of reviewing the literature done by Lehmann *et al.* (2002;234), about 25 different methods of assessment for acne severity were identified, ranging from the photographic comparisons, lesion counting on all or part of the face and the comparison to text description. In addition to the actual grade of the acne, one should take into account the extent of involvement. The presence of scarring should also be noted and a patient with scarring would immediately be placed in a more severe category than one without scarring (both physical and emotional scarring), because this will certainly influence the decision on the treatment method (Sinclair & Jordaan, 2005:885).

Even with these grading systems in use at this stage there are still certain assessment-related needs that have to be attended to. One of these is an approach that can be used in the office or clinic setting and will be easy to use, will require little time, will be accurate, and will not require complicated instrumentation. Another need is an approach that can be used by clinical investigators as a more sensitive indicator of acne severity, used for more accurate classification by doctors (dermatologists) (Witkowski & Parish, 2004:396).

2.3.4 Acne scarring

When acne reaches the inflammatory stage a number of different inflammatory lesions develop which can be painful, unsightly and in 30% of patients it will lead to scarring (Cunliffe, 1998:9).

Acne scarring is a consequence of the damage that occurs in and around the pilosebaceous follicle during inflammation (Tsao *et al.*, 2002:53). However, the precise mechanisms and factors which govern the initiation and exacerbation of inflammation are not fully known. It is already known that there are both humoral and cellular immune components which correlate with the severity of the disease, and that antigens of *Propionibacterium acnes* play a central role in developing scars. Therefore, the type of immune response of patients predisposed to scarring may be different to those who do not scar. To date there is only one study on this topic (Holland *et al.,* 2004:73).

The most recent study made by Jacob *et al.* (2001:109), on the classification of acne scarring divided acne scarring into three basic types: ice-pick scars, rolling scars, and boxcar scars. Although many scar types have been described, the lack of consistency in scar description precludes accurate comparison among studies. There are certainly subtle variations within each subtype, but remarkable consistency has been found within this new simple classification system for categorising scars. It also has the atvantage that most of the acne scars can be classified in this way.

Although three kinds of scars are identified there are actually five types of scars, the top and bottom scars being different kinds of scars:

- Postinflammatory hyperpigmentafion or macules
- Ice pick scars
- Crateriform "boxcar" scars
- Shallow "rolling" scars
- Hypertrophic scars and keloids

Macules or "pseudo-scars" are flat, red or reddish spots forming the final stage of most inflamed acne lesions. This represents post-inflammatory hyperpigmentation and erythema. After an inflamed acne lesion flattens, a macule may remain to "mark the spot" for up to 6 to

12 months. When the macule eventually disappears, no trace of it will remain—unlike a scar (AcneNet, 2008; Tsao *et al.*, 2002:53).

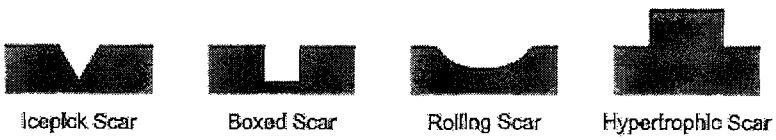

Figure 2.6: Simple illustration of acne scars (Acne Guide, 2008)

Icepick scars (Fig. 2.6), or deep pitted scars, are narrow (<2 mm), deep, sharply marginated epithelial tracts that extend vertically to the deep dermis or subcutaneous tissue, resembling a small hole. The surface opening is usually, but not always, wider than the deeper infundibulum as the scar tapers from the surface to its deepest apex. Their depth is below that reached with conventional skin resurfacing options (Jacob *et al.*, 2001:110; Tsao *et al.*, 2002:54).

Perhaps the most common acne scar is the boxcar scar (Fig. 2.6) which is a round to oval depression with sharply demarcated vertical edges. They are clinically wider at the surface than icepick scars and do not taper to a point at the base. They may be shallow (0.1-0.5 mm) or deep (≥0.5 mm) and are most often 1.5 to 4.0 mm in diameter. A fibrotic lesion is present, with extension of the fibrosis into the dermis and subcutaneous fat resulting in a firm, semi-rigid scar. Shallow boxcar scars are within the dermal reach of skin resurfacing treatments (such as laser skin resurfacing), but deeper boxcar scars are resistant to improvement in the absence of full-thickness treatment of the scar (Jacob *et al.*, 2001:111; Tsao *et al.*, 2002:53-54).

Rolling scars (Fig 2.6) are soft, distensible, depressed scars, with a slightly wrinkled superficial base. These scars present as shallow undulations and may be subtle, but often become more noticeable with lighting changes or as the patient moves his or her head. Rolling scars can be small (less than 1 cm) or large (greater than 1 cm). Often, patients will have several individual rolling scars that coalesce to form a larger area of scarring (Tsao *et al.*, 2002:54).

The scars caused by increased tissue formation are called keloids or hypertrophic scars (Fig. 2.6). The word hypertrophy means "enlargement" or "overgrowth." Both hypertrophic and keloid scars are associated with the overproduction of collagen, a response to skin cell injury. The excess collagen becomes piled up in fibrous masses, resulting in a

characteristic firm, smooth, usually irregularly-shaped scar. The typical keloid is 1 to 2 millimetres in diameter, but some may be 1 centimetre or larger. These scars persist for years, but may diminish in size over time (AcneNet, 2008).

An individual may present with one type of scar or a combination of scar types, but treatment must be tailored to the type of scarring present, because treatment differs for the diverse types of acne scars (Tsao *et al.*, 2002:54).

2.3.5 The impact of acne on the quality of life

Quality of life is the degree of enjoyment or satisfaction experienced in everyday life and several studies using validated instruments have been completed evaluating the quality of life in patients with acne (Hanna *et al.*, 2003:8).

Yazici *et al.* (2004:238) found that disease-specific quality of life in patients with acne had the following effects:

- Firstly, irrespective of the degree of severity, patients with acne are at increased risk for anxiety and depression compared to the normal population.
- Secondly, acne negatively affects quality of life, and the greater the impairment of quality of life due to acne, the greater the level of anxiety and depression.

In a study conducted by Dreno *et al.* (2003:167), it was indicated that about one in five consultations at dermatologists were in relation to acne disorders with mild and moderate *acne vulgaris* the most common form of acne seen in these visits, at almost 60% of patients, far more frequent than nodular acne (only about 10% of the patients), emphasising that patients want treatment in a less severe stage of the disease. A study done by Mosam *et al.* (2005:5-7), in South Africa, on how the people of lower income groups react to acne, showed the different perceptions about acne and the effect of acne on their quality of life. Patients' perceptions of the severity of their acne were as follows: 14.0% thought their acne was mild, 45.8% moderate and 40.2% severe. Patients' perception of their acne severity was not associated with the physician rating using the Global Acne Grading scale. Using the Global Acne Grading scale, 1% had no lesions, 45.8% had mild, 45.8% had moderate and 7.5% had severe acne. This indicates that the South African patients with *acne vulgaris* suffer significant psychological distress, experiencing acne more severe than the specific grading system indicated, indicating the effect acne has on their quality of life.

Ozolins *et al.* (2004:1293) found that participants in a study evaluating different cures were willing to pay much more for a cure than for the treatment they had received and were also willing to pay more for a cure at the end of the study than at the start. These findings suggest that they valued a cure more highly after experiencing limited success.

People experience acne worse than what it really is and they are willing to pay more if they experience limited success. This emphasises the importance of acne to the general public and the effect it has on the lives of the people suffering from it. Even though acne is not at all a life threatening disease the underlying psychological distress affects the quality of life negatively.

Acne has been implicated in psychiatric and psychological processes more than most other dermatological conditions and these significant non-dermatological effects are because of the specific population affected (adolescents), distribution of lesions (the facial area), misperceptions regarding etiology of the condition, and the strong emphasis placed on physical appearance (Hanna *et al.,* 2003:8). Even in impoverished communities where the health care system is burdened with infectious disease, the consumers still place a premium on image (Mosam *et al.*, 2005:8). According to Jordan *et al.* (2005:191) patients with severe acne lose approximately 15% of their physical and psychological quality of life, while patients with moderate and mild acne lose approximately 3% and 2%, respectively.

It is important to note that not all patients who develop acne experience psychiatric or psychological complications or any alteration in quality of life. However, the scientific literature clearly illustrates that these complications occur more frequently in patients suffering from *acne vulgaris* (Gupta et al., 1998:451). The treating physician should consider these factors when selecting an appropriate treatment. Addressing non-dermatological effects of acne allows the physician to treat more than merely the skin condition. *Acne vulgaris* is a common skin disease with potential complications that are more than skin deep (Hanna et al., 2003:8).

2.3.6 Acne therapies

There are many different types of treatments and in table 2.3 the different effects of these different acne therapies are described according to the four categories identified as the best mechanism of action areas to focus on when using acne therapy.

Table 2.3: Acne therapies and their associated activities (Gollnick, 2003:1590; Leyden, 2003:S202).

Therapy	Keratolytic/ comedolytic	Antimicrobial	Anti-inflammatory	Sebosuppressive
Topical				
Tretinoin	Strong	Weak	None	None
Isotretinoin	Strong	Weak	Weak	None
Adapalene	Strong	Weak	Moderate	None
Tazarotene	Strong	Weak	None	None
Azelaic acid	Moderate	Moderate	Weak	None
Benzoyl peroxide	Weak*	Strong	None	None
Topical antibacterial agents	Weak*	Strong	Weak	None
Systemic				
Oral antibacterial agents	Weak*	Strong	Moderate	None
Isotretinoin	Strong	Moderate*	Moderate	Strong
Oral contraceptive	Moderate	None	None	Strong

*Indirectly

Only isotretinoin has an effect on all four areas of mechanism of action according to table 2.3. In the following sections the different kinds of acne treatments are discussed, with the exception of oral retinoids (isotretinoin).

2.3.6.1 Antibacterial agents/antibiotics and benzoyl peroxide

The Global Alliance to improve outcomes in acne evaluated the present and past research done on antibacterial agents/antibiotics and benzoyl peroxide in acne to reach consensus on the effects and guidelines of acne treatment (Gollnick *et al.*, 2003:S1).

The Consensus of the Global Alliance was the following: Antibiotic Therapy Primarily:

- Affects inflammatory lesions
- Oral and topical antibiotics usually should not be used as monotherapy
- Antibiotics are generally well tolerated, but are associated with rare instances of severe adverse events
- Antibiotics should be combined with topical retinoids to enhance efficacy against comedones and inflammatory acne lesions
- Benzoyl peroxide alone significantly improves inflammatory acne
- Topical benzoyl peroxide or azaleic acid treatment may be added to antibiotics to reduce the potential of developing *P. acnes* resistance (Gollnick *et al.*, 2003:S15)

The antibacterial agents/antibiotics are the most frequently used type of drug in the treatment of acne (Sinclair & Jordaan, 2005:885). They can be used both topically and systemically, the latter being far more effective. It is generally accepted that antibiotics are largely abused in the management of acne and many of the problems experienced with the use of antibiotics are due to inappropriate use of these preparations, the major problem being, resistance to antibiotics (Strauss *et al.*, 2007:654). Propioniobacteria has already been found to be resistant to one or more antibiotics in the UK, France, Germany, Japan, New Zealand and USA (Ross *et al.*, 2001:345).

Different classes of antibiotics are used in acne management. The most frequently used are the tetracyclines, especially doxycycline, lymecycline, minocycline and the older first-generation tetracyclines. Erythromycin is also frequently used, both topically and systemically, and the same applies to clindamycin. Co-trimoxazole is also commonly used, as it is inexpensive and often highly effective. As a rule the penicillins are ineffective in this context (Sinclair & Jordaan, 2005:885). Although erythromycin is effective, use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children under 8 years of age because of the potential for damage to the skeleton or teeth). The development

of bacterial resistance is also common during erythromycin therapy (Strauss *et al.*, 2007:654).

Treatment with antibiotics should be limited to a maximum of 4 months as there would be little improvement thereafter and also because antibiotic resistance will become more apparent after 4 months of treatment (Sinclair & Jordaan, 2005:886).

Benzoyl peroxide and combinations with erythromycin or clindamycin are effective acne treatments. The combination of erythromycin and benzoyl peroxide is not affected by bacterial resistance, whereas the clinical efficacy of oral teracyclines is compromised by pre-existing propionibacterial resistance (Osolins *et al.*, 2004:2193). Topical antibiotics (e.g., erythromycin and clindamycin) are effective acne treatments; however, the use of these agents alone can be associated with the development of bacterial resistance (Strauss *et al.*, 2007:653), therefore combination therapy is very important to prevent bacterial resistance.

Differences in cost-effectiveness between regimens are large. Benzoyl peroxide as monotherapy was the most cost-effective regimen for mild to moderate facial acne and was 12 times more cost-effective than minocycline. With appropriate management of the irritant potential, it represents the best value antimicrobial for first-line use (Ozolins *et al.*, 2004:1294).

2.3.6.2 Topical retinoids

The Global Alliance to improve outcomes in acne reached consensus about the following: (Gollnick *et al.*, 2003:S5) Topical retinoids have multiple anti-acne actions as indicated below:

- Inhibit the formation of and reduce the number of microcomedones (precursor lesions)
- Reduce mature comedones
- Reduce inflammatory lesions
- Promote normal desquamation of follicular epithelium
- Some may be anti-inflammatory
- Likely to enhance penetration of other drugs

- Likely to maintain remission of acne by inhibiting microcomedo formation, thus preventing new lesions

The different topical retinoids available, namely tretinoin, adapalene, isotretinoin (topical form), and tazarotene, have similar efficacy but share a common side-effect in the form of initial irritation on application. Of these preparations, adapalene seems to be the one least prone to cause significant irritation (Cunliffe *et al.*, 1998:51) and that is why some physicians consider it preferable to start treatment with adapalene and if improvement is not observed, to then consider the application of tretinoin, isotretinoin, or tazarotene (Rigopoulos *et al.*, 2004:410).

In a survey done by Balkrishnan *et al.* (2003:173) in the United States from 1990 to 1999, it was found that of the 54.2 million *acne vulgaris* visits, topical retinoids were prescribed 35.3% of the time. Dermatologists prescribed significantly more topical retinoids than non-dermatologists (39.4% versus 23%) and even if there has been an increasing in prescribing of topical retinoids for acne over the past decade, there is still a distinct underutilisation of topical retinoids for treatment of *acne vulgaris* by dermatologists and non-dermatologists.

The Global Alliance recommended that topical retinoids should be used as the primary treatment for most forms of *acne vulgaris* and used early for best results. It should be applied to the entire affected area and used as the essential part of maintenance therapy and for a better effect it should also be combined with antimicrobial therapy when inflammatory lesions are present. Combination therapy is better than any of these agents as monotherapy (Gollnick *et al.*, 2003:S9).

According to Zaenglein & Thiboutot (2006:1188) the recommendation now is that acne treatments should be combined to target as many pathogenic factors as possible.

- The topical retinoid is the foundation of treatment for most patients with acne, because retinoids target the microcomedo, the precursor to all acne lesions. Retinoids also are comedolytic and have intrinsic anti-inflammatory effects, thus targeting 2 pathogenic factors in acne (Gollnick *et al.*, 2003:S9; Zaenglein & Thiboutot, 2006:1188).

- Combining a topical retinoid with an antimicrobial agent targets 3 pathogenic factors, and clinical trials have shown that combination therapy results in significantly faster and greater clearing as opposed to antimicrobial therapy alone (Leyden, 2003:S208; Zaenglein & Thiboutot, 2006:1188).

- Oral antibiotics should be used only in moderate-to-severe acne, should not be used as monotherapy and should be discontinued as soon as possible (after 4 months) (Zaenglein & Thiboutot, 2006:1188).

- Because of their effect on the microcomedo, topical retinoids also are recommended as an important facet of maintenance therapy (Sincliar & Jordaan, 2005:888; Zaenglein & Thiboutot, 2006:1188).

In general, all but the mildest cases of acne vulgaris will obtain maximum benefit from a topical combination of retinoids and antimicrobials started early in the course of disease. Once good control has been achieved, the antimicrobial can be withdrawn, and the benefit maintained with the retinoid alone. Clinical experience suggests that adapalene gel is a very effective agent for use in such combination regimens (Leyden, 2003:S203).

In a 13-year period study from 1990 to 2002 Thevarajah *et al.* (2005:225) found that there were significant declines in the likelihood of prescribing antimicrobial products, whereas there were significant increases in the likelihood of prescribing topical and systemic retinoid agents, emphasising the growing importance of retinoids.

2.3.6.3 Hormonal treatment

Hormonal treatment plays a very important role in acne treatment, especially in the female gender. The Global Alliance reached consensus about the following (Gollnick *et al.*, 2003:S25): Hormonal therapy:

- Excellent choice for women who need oral contraception for gynaecologic reasons

- Use early in female patients with moderate to severe acne or with SAHA symptoms

- Useful as a component of combination therapy in women with or without endocrine abnormalities

- Sometimes used in women with late-onset acne

Acne is an androgen-dependent condition and in females the androgens can be effectively blocked or reduced, often leading to significant improvement in or clearing of the condition (Katsambas & Papakonstantinou, 2004:415). It represents an excellent choice for women who need oral contraception and should be used early for patients with moderate to severe acne who also have signs of androgen over activity (Seborrhoea, Acne, Hirsutism,

Androgenic alopecia (SAHA)). It is useful in combination treatment, in women with late-onset acne and in patients with prominent premenstrual acne flares (Sinclair & Jordaan, 2005:888-889)

Hormonal therapy for acne may consist of

- anti-androgens (cyproterone acetate, chlormadinone acetate, spironolactone, drospirenone, desogestrel, flutamide);
- agents that suppress ovarian and adrenal androgen production (estrogens, oral contraceptives (containing cyproterone acetate), cyproterone acetate, gonadrotropin-releasing hormone agonists, low-dose glucocorticoids); and
- possibly in the future there will be inhibitors of enzymes that are involved in androgen metabolism in the skin. (Gollnick et al., 2003:S20; Shaw, 2002:573; Thiboutot, 2001:60)

Although an indication for hormonal therapy is hyperandrogenism, women with normal serum androgen levels also respond well to treatment (Thiboutot, 2001:60) and that is why hormonal treatment is always a good option for treating acne in females.

Some authorities feel that the combination of a topical retinoid with hormonal therapy brings about a much quicker response than hormonal treatment alone and should be regarded as an acceptable treatment option (Sinclair & Jordaan, 2005:889).

2.3.6.4 Usage of acne treatments

Much has been said on acne therapy and which treatments are best for the different severity forms of acne. Leyden (2003:S208) has a proposed treatment guideline which is in close correlation with the Global Alliance (see figure 2.7).

Acne is a highly treatable disease. The use of combination therapies or systemic isotretinoin as mono-therapy have the potential to improve treatment by producing greater and faster results by simplifying management for the dermatologist, leading to greater patient satisfaction and compliance with therapy (Leyden, 2003:S208).

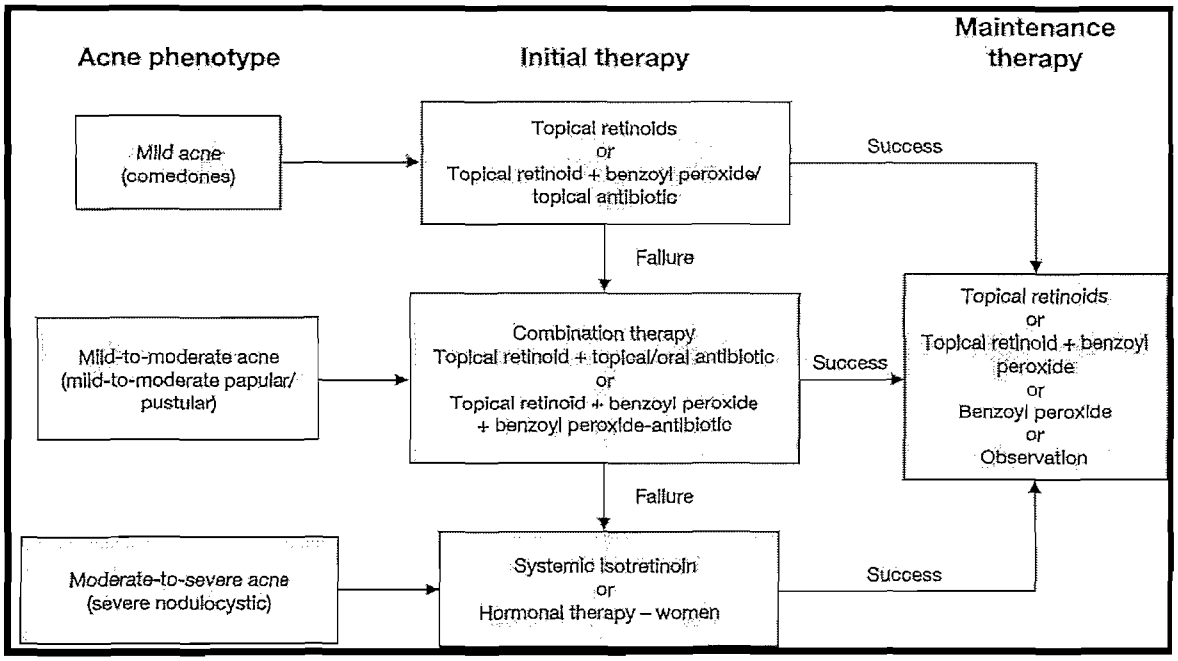

Figure 2.7: Proposed algorithm for the management of acne vulgaris in dermatologic clinical practice (Leyden, 2003:S208).

Perhaps the most important tool in the effective management of acne concerns the clinician's ability to educate and listen to the patient, working together to provide the best treatment strategy for that individual and in doing so it will ensure better compliance and thus better outcomes (Zaenglein & Thiboutot, 2006:1197).

2.4 ISOTRETINOIN

2.4.1 Introduction

The physical and emotional challenges facing acne patients place great pressure on dermatologists to provide an effective and safe treatment for patients with severe acne and those with less severe acne that obtain scars or are associated with marked psychological distress (Cooper, 2003:97).

Isotretinoin has revolutionised the treatment of acne when it was introduced in 1982 and became available in South Africa in 1984. Systemic isotretinoin (this section only refers to systemic isotretinoin) still remains the most effective anti-acne treatment, as it is the only treatment that affects all four pathophysiological factors implicated in the acne process (Presbury *et al.*, 1997:1410). Isotretinoin is one of the most effective and widely prescribed drugs in dermatologic practice and although there is consensus regarding the extraordinary efficacy of isotretinoin in the treatment of acne vulgaris, there is still a great concern about the toxicity of this agent and of the retinoids as a class of drugs. Furthermore, there is little

basic knowledge about the mechanism of action of either the therapeutic or the toxic effects of isotretinoin or the other retinoids (Bickers & Saurat, 2001:S125).

The rise in antibiotic resistance over the last decades (Coates *et al,* 2002:840) had a big impact and influence in the numbers of isotretinoin usage. A study done in the United States by Wysowski *et al.* (2002:508) indicated that the median annual number of prescriptions for isotretinoin in 1983 to 1992 was just over 800,000 per year; between 1992 and 2000, the number of prescriptions increased 2.5 fold (250%) to nearly 2 million in year 2000, with only a 9% increase in the resident population aged 15 to 19 years over the time period of 1995 to 2000 and an increase of 4% in the population aged 20 to 24 years. These findings emphasise the importance of isotretinoin in acne disorders. Thevarajah *et al.* (2005:227) also agreed with this significant increase in prescriptions for isotretinoin during their 13-year study period.

There are many factors that could have resulted in the increase in prescriptions for isotretinoin. Firstly, the increased patient visits during isotretinoin therapy could be attributed to closer physician supervision. Secondly, more people have health insurance that includes a prescription benefit that would defer most of the cost substantially. Thirdly, isotretinoin may have been prescribed in less severe or recalcitrant acne as the therapeutic benefits are more widely known (Thevarajah *et al.*, 2005:227). None the less, isotretinoin usage is increasing and together with that the importance of the drug.

2.4.2 Indications

It is primarily indicated as an agent for patients with severe nodulocystic acne. However, increasing clinical experience has made it clear that it can also be of benefit to patients with moderate or even mild acne that is resistant to long-term oral or topical treatment, or acne associated with severe scarring or significant psychological complications and extensive acne involving the face and trunk (Katsambas & Papakonstantinou, 2004:414). The Global Alliance to improve outcomes in acne, reached consensus over the following recommendations (Gollnick *et al.*, 2003:S29):

- Severe nodulocystic acne/severe acne variants
- Inflammatory acne with scarring
- Moderate to severe acne frequently relapsing, where repeated or prolonged courses of systemic antibiotics are needed

- Acne with severe psychological distress (dysmorphophobic patients)
- Moderate to severe acne unresponsive to treatment with:
    - Three months of combination treatment including systemic antibiotics
    - Four cycles of anti-androgen containing hormonal treatment
- Gram-negative folliculitis

In relation to this recommendation the indication for isotretinoin usage in South Africa is mainly for the management of intractable acne, but may also be effective in controlling kretinisation disorders such as the ichthyoses and keratosis follicularis. Use should, however, be restricted to severe acne unresponsive to conventional therapy (Gibbon *et al.*, 2005:194).

According to Wysowski *et al.* (2002:507), between 1993 and 2000, the proportion of isotretinoin treatment for severe acne declined from 63% to 46%, whereas the proportion of treatment for mild and moderate acne increased from 31% to 49%, making it more common to prescribe isotretinoin for milder cases of acne. There is no doubt that it is the drug of choice for severe acne, with benefits far outweighing the risks involved. It has, however, become fashionable to use the drug for less severe cases where other more conservative treatments may have been successful. Isotretinoin is often prescribed under pressure from patients, but physicians should nevertheless adhere to prescribed indications for the use of this drug to prevent medico-legal consequences (Sinclair & Jordaan, 2005:889).

Although isotretinoin is only indicated for acne, it is being used in other circumstances. In addition to the treatment of acne, isotretinoin has been demonstrated to be effective in the treatment of disorders of cornification and in chemoprevention of skin cancer in high risk individuals who are actively developing multiple basal cell and squamous cell carcinomas, which include those patients with xeroderma pigmentosum, the nevoid basal cell carcinoma syndrome or those who are immunosuppressed (e.g. individuals receiving immunosuppressive agents to prevent organ transplant rejection) (Goldsmith *et al.*, 2004:904). In the United States a study done on the diagnosis associated with isotretinoin, acne unspecified presented 97% of mentions with rosacea, 1% of the time, and a variety of other diagnoses (e.g. malignant neoplasms, dermatitis and other dermatologic conditions) in the remaining 2% (Wysowski *et al.*, 2002:507-508). Indications for isotretinoin are widely spread in the dermatological field but acne is still the main reason for its use.

2.4.3 Mechanism of action

The exact mechanism of action is not fully known, but it is known that oral isotretinoin is a retinoid preparation that decreases the size and secretion of the sebaceous glands, normalises follicular keratinization and prevents the formation of new comedones, indirectly inhibits *P. acnes* growth via changes of the follicular milieu, and exerts an anti-inflammatory effect (Gollnick *et al.*, 2003:S26). It is known that isotretinoin is a vitamin A derivate and according to recent research, synthetic retinoids inhibit proliferation of sebocytes and can also reduce lipid synthesis. It has been shown that isotretinoin causes cell cycle arrest and induces apoptosis in sebocytes in vitro by a retinoic acid receptor (RAR)-independent pathway (Nelson *et al.*, 2006:2178).

Oral isotretinoin is the most effective sebosuppressive agent. It decreases sebaceous gland volume by 90% and sebum production by 70–90%. Such sebostatic activity is dose-dependent, but once treatment is discontinued, sebum content returns to normal and the sebum quantity stays at approximately 40% of the basal value (Kaymak & Ilter, 2006:1257).

2.4.4 Dosing/Optimum use of isotretinoin and the clinical effect

The approved dosage range is 0.5 to 2.0 mg/kg per day, although the use of a dosage exceeding 1.0 mg/kg per day is very rarely used. The 'Recommendations of the Global Alliance' also agreed that isotretinoin dosage should not be below 0.5 mg/kg per day, but should not exceed 1mg/kg per day, in order to limit side-effects (Gollnick *et al.*, 2003:S29).

The duration of treatment and the daily dose taken are determined by the body weight of the patient. The drug is usually given over a 16-24 week course, with the aim for a minimum target of 120 mg per kg as a total cumulative dose but this can be increased to 150 mg per kg if a satisfactory result has not been achieved once 120 mg/kg has been reached. Drug absorption is greater when the drug is taken with food (especially fatty food). The initial flaring of acne and the response of adverse effects after starting isotretinoin treatment can be minimised with an initial dose of 0.5 mg/kg per day or less, and if the response is slight, increase the dose to a maximum of 1.0 mg/kg per day. Alternatively, lower doses can be used for longer time periods, as long as a total cumulative dose of 120 to 150 mg/kg is reached (Strauss *et al.*, 2007:656; Amichai *et al.*, 2006:644; Sinclair & Jordaan, 2005:890; Gollnick *et al.*, 2003:S29; Gibbon *et al.*, 2005:195).

A few studies have been done on the treatment of acne with low-dose (20 mg/d) and intermittent isotretinoin, with high success rates, but their studies were done on mild and

moderate acne and the success of these treatment regimens on severe acne has not been tested, the main indication for isotretinoin (Akman *et al.*, 2007:473; Amichai *et al.*, 2006:644; Kaymak & Ilter, 2006:580). South African dermatologists felt that the so-called pulse-dosage regimen, where 0.5 mg/kg is taken daily on the first seven days of each month, is usually free from side-effects, except for the teratogenic effect, and highly effective for patients who relapsed after a previous full course of this drug, as well as for older patients with chronic, indolent, resistant acne (Sincliar & Jordaan, 2005:890).

A special set of circumstances in which low-dosage continuous isotretinoin may be used, involves young teenagers with very severe comedonal acne. These patients respond very poorly to topical comedolytic agents initially, and a 4-6 month course of 10-20 mg of isotretinoin per day can lead to prompt clearance of these lesions, whereafter maintenance with topical retinoids should be highly effective (Sincliar & Jordaan, 2005:890).

The testing of the clinical effect of isotretinoin shows a 91% "improvement" rate and 9% "partial healing" rate on all patients responding to treatment in the most recent study done by Kaymak and Ilter (2006:580) on results of isotretinoin therapy. In a meta-analysis of effectiveness in the literature done by Wessels *et al.* (1999:784), they indicated that there was consistent evidence of a high success rate, between 84.2% and 86.7%, when an average treatment period of 17.9 weeks (4 months), with dosage of isotretinoin from 0.33 to 1 mg/kg/day was followed.

2.4.5 Adverse effects/events

Isotretinoin causes numerous side-effects, some of which are serious, but most of the side-effects are less serious. Most patients experience the period on this drug as very unpleasant, but they endure the side-effects because they experience the benefits very soon after treatment has been started (Sinclair & Jordaan, 2005:889).

2.4.5.1 Common adverse effects

Most of these effects are dose-related and the most common are those of hypervitaminosis A (e.g. dryness of the mucosa, Table 2.4, (isotretinoin is a vitamin A derivate)). These adverse effects are more troublesome during the first few months of therapy and are usually responsive to topical moisturisers. Only in a small number of patients are they severe

enough to require treatment with topical steroids or antibiotics (Katsambas & Papakonstantinou, 2004:414: McLane, 2001:S193).

Table 2.4: Side-effects of isotretinoin therapy (McLane, 2001:S192-S193; Presbury *et al.*, 1997:1412)

Side-effect	Incidence	Management
Dry chapped lips (cheilitis)	>90%	Frequent lip balm
Dry skin and itching	±80%	Avoid drying soaps. Apply emollients after bath (e.g. aqueous cream).
Dry eyes/conjunctivitis	±35-40%	Use artificial tears or eye ointment. If contact lenses cause discomfort glasses should be worn.
Rash or redness (face)	<35%	Emollients
Dryness in mouth or thirst	±30%	Frequent fluids
Nose bleeds	±20%	More frequent in winter. Apply petroleum jellies or thicker lotions (e.g. vaseline) to the insides of the nostrils.
Joint and muscle pains	<20%	Avoid any strenuous exercise. Take analgesics.
Temporary hair thinning	<10%	Should return to normal within a year.
Photosensitivity	±5%	Sunscreen of ≥SPF 15
Headache	Rare	If minor, analgesics. If severe or persistent, lower dose.
Night blindness	Rare	Make sure your vision is not affected.

Cheilitis is the most common manifestation and occurs in virtually all patients who receive isotretinoin therapy. This cheilitis generally requires continual application of topical emollients during therapy (Ellis & Krach, 2001:S152). Women generally complained more about the side-effects of dry skin than men do (Kaymak & Ilter, 2006:577).

Some of the adverse events, such as muscle or joint aches, were reported by approximately 50% of the patients when they were asked specifically about these events but were reported spontaneously by only approximately 15% of the patients, making it difficult to precisely evaluate the incidence of certain side-effects (McLane, 2001:S193).

In the additional study done on the side-effects of isotretinoin, more than half of the patients had exacerbation of their acne in the first month of treatment (Kaymak & Ilter, 2006:577), something that does occur frequently and could be avoided if dose reductions are done.

Other recommendations of the 'Food and Drug Association of America' (FDA) include that users of isotretinoin should not drive at night until they know if isotretinoin has affected their vision; all cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, should be avoided during isotretinoin treatment and for at least 6 months after therapy has been discontinued. Isotretinoin can increase the chance of scarring from these procedures" (FDA, 2005). Patients should be told to avoid sunlight and ultraviolet lights as much as possible, because photosensitivity is a common side-effect and patients must be informed to stay out of the sun and use sunscreen (SPF $\geq$15) if they go outdoors (tanning machines use ultraviolet lights and should not be used) (FDA, 2005; Persbury *et al.,* 1997:1412).

None of these common side-effects poses a big problem to the use of isotretinoin in acne therapy. The more serious side-effects like teratogenicity, depression, liver and blood effects and a few unusual side-effects are the reasons why isotretinoin is not used more regularly.

2.4.5.2 Teratogenicity

Isotretinoin used in women of child-bearing age is a very important public health issue because of the teratogenicity of the drug which includes the risk of spontaneous and elective abortions, and children with major malformations that will require continuous health care services throughout their lifetime. It is an even more important problem due to the fact that it is preventable (Bèrard *et al.*, 2007:197). All doses of isotretinoin have a teratogencicity effect. The drug is a Category X drug, meaning that it must be avoided under all circumstances during pregnancy. It is important to ascertain that female patients are not pregnant before initiating treatment and to ensure that they do not fall pregnant while on isotretinion treatment and until one month after discontinuation of therapy (Gibbon *et al.,* 2005:194; Meadows, 2001:2)

About 40% of infants exposed to isotretinoin in the first trimester will have major malformations (Table 2.5). In addition, children exposed in-utero who are spared from major malformation may still be affected by cognitive deficits (Koren *et al.*, 2004:1567). To emphasise the importance of strict regulation of isotretinoin use, a recent study was done on 158 pregnancies detected while using isotretinoin. Sixty-eight pregnancies (43%) had began

before the start of the isotretinoin therapy and 90 (57%) occurred during isotretinoin treatment. An additional 52 pregnancies were diagnosed in the first month following isotretinoin discontinuation. Of the 90 women who became pregnant while exposed to isotretinoin, 76 terminated the pregnancy (elective abortions: 84.4%), three had a spontaneous abortion (3.3%), two had trauma during delivery resulting in neonatal deaths (2.2%) and nine had a live birth (10.0%) of which one (11%) had a congenital anomaly of the face and neck diagnosed at 3 years. The remaining nine babies had no congenital malformations reported during the first 3 years of life (Bèrard *et al.*, 2007:200).

Table 2.5: Characteristics of isotretinoin embryopathy (Koren et al., 2004:1567)

Areas	Defects
• Central nervous system:	microcephaly with hydrocephaly
• Face and head:	absence or reduced size of outer ear and ear canal
• Heart:	defect of aortic arch, double outlet of right ventricle
• Thymus:	hypoplasia, aplasia

In a survey done in Europe (Denmark) dermatologists requested a blood test (for reasons of liver and blood effects, refer to section 2.4.5.3) 98% of the time before prescribing isotretinoin, whereas only 85% asked their patients to perform a pregnancy test (only including fertile female patients). It appears that some dermatologists pay less attention to the teratogenic potential of the drug (Wildfang *et al.*, 2002:151).

After a FDA review of pregnancy exposures to isotretinoin, Roche® (the original/innovator pharmaceutical company manufacturing isotretinoin) launched the Pregnancy Prevention Program (PPP) in late 1988 to further educate women using isotretinoin and their physicians about the dangers. Experts said the PPP is a significant programme that had prevented many pregnancies and is the first of its kind initiated by a pharmaceutical company (Meadows, 2001).

Countries across the world approach the prescribing and dispensing of isotretinoin in different ways, refer to table 2.6, from the US with their strict programmes, the UK where only dermatologists may prescribe isotretinoin to Mexico and Venezuela with no programmes and where even OTC (over-the-counter) purchasing is possible.

Table 2.6: International variation in the systems to prevent pregnancy exposures to isotretinoin (Honein *et al.*, 2004:1074)

Country	Prescribers	Programme for prevention of exposed pregnancies
US	Any medical doctor	Yes PPP (Accutane®), 1988–2001 S.M.A.R.T.⇔ (Accutane®), 2002–2006 iP.L.E.D.G.E⇔(Accutane®), 2006-present S.P.I.R.I.T.⇔ (Amesteem®), 2002 I.M.P.A.R.T.⇔ (Sotret®), 2003 A.L.E.R.T.⇔ (Claravis®), 2003
Canada	Any medical doctor	Yes PPP, 1988–present
Argentina	Any medical doctor	No
Brazil	Any medical doctor	No
France	Any medical doctor	No
Italy	Any medical doctor	No
New Zealand	Any medical doctor, but only prescriptions from dermatologists are fully funded	No
Australia	Dermatologists only	No
Denmark	Dermatologists or hospitals only	No
Ireland	Dermatologists only	No
Sweden	Dermatologists only	Individually licensed patents from 1984–1988; licensed only dermatologists to prescribe after 1988
UK	Dermatologists only	No
Bolivia	OTC purchase possible	No
Mexico	OTC purchase possible	No
Venezuela	OTC purchase possible	No

A.L.E.R.T. = Adverse Event Learning and Education Regarding Teratogenicity⇔; **I.M.P.A.R.T.** = Isotretinoin Medication Program Alerting you to the Risks of Teratogenicity⇔; ***PPP*** = Pregnancy Prevention Program; **S.M.A.R.T.** = System to Manage Accutane Related Teratogenicity⇔; **S.P.I.R.I.T.** = System to Prevent Isotretinoin-Related Issues of Teratogenicity⇔; **iPLEDGE** = Most recent pregnancy prevention programme.

A big problem in the USA is that none of the guidelines implemented to prevent pregnancy from occurring while on isotretinoin therapy, made any notable impact over a 19-year study period done by Bèrard *et al.* (2007:203). This is the main reason why the most recent programme (called iPLEDGE) was introduced. Other reasons include the generic isotretinoin compounds which entered the market in 2002 (this made isotretinoin more affordable) and risk management programmes that have not been centralised thus far. These factors also contributed to the FDA deciding to launch this integrated isotretinoin risk management programme (iPLEDGE, 2006) for all isotretinoin compounds in the USA (Bèrard *et al.*, 2007:197).

The iPLEDGE programme was fully implemented on 1 March 2006. This programme is robust in that it includes wholesalers, pharmacies, prescribers and patients, all of whom must agree to the requirements of the programme in order to have access to isotretinoin (Honein et al., 2007:7). This iPLEDGE programme is the largest risk-minimisation programme that has ever been implemented for a drug (Honein *et al.*, 2007:11) and it seems likely that the iPLEDGE programme will reduce the utilization of isotretinoin. Reducing total isotretinoin usage should, in itself, reduce the number of fetal exposures, but rates will not go down without committed and adherent patients (Cheetham *et al.*, 2006:447).

In a study done in the early nineties by Smart and Walters (1994:499), in South Africa, they found that contraception is used by less than half (48.25%) of female patients using prescribed isotretinoin. The methods of contraception used in the total female population consist of the depot contraceptive and the intrauterine device, used by 0.81% and 2.96% respectively. The oral contraceptive was used by 36.39% of women, and 8.09% practised other forms of contraception (e.g. sterilisation, condoms and vasectomy of partner). In the remaining 51.75%, contraception was deemed unnecessary. This group included patients who were not sexually active, had given informed consent or had religious objections to contraception. Although this is a study done in the early nineties, it is more than likely still the situation today.

In the most recent Acne Guidelines of South Africa (2005), the following guidelines were given: - the patient should adhere to strict contraception for a month before the start of treatment, undergo a negative pregnancy test thereafter and start medication on the third day of her next menstrual period. Effective contraception should continue through-out therapy up until one month after taking the last tablet in the isotretinoin course. Monthly negative tests are recommended in South Africa but are compulsory in the USA. The patient should be fully aware of the risks, and should sign written consent for use of the drug, indicating her understanding that a therapeutic abortion would be compulsory should she fall pregnant during treatment (Sinclair & Jordaan, 2005:889; Presbury *et al.*, 1997:1412). In an international study on the fetal exposure to isotretinoin they came to the conclusion that the main reason for pregnancies occurring while women were on isotretinoin was because they had not been informed about the importance of contraceptive use while on isotretinoin (Garcia-Bournissen, 2008:126).

In summary it can be pointed out that every effort should be made to ensure the reduction in the rate of pregnancies in women taking isotretinoin. With this in mind, it is vital to consider the characteristics of the specific country where the drug is being prescribed and of the individual who will use it. If isotretinoin is prescribed to an individual or in a society that would

not tolerate or facilitate access to therapeutic abortions, the potential for failure of any prevention programme is large, as no programme has been shown to reduce such pregnancies to zero. Countries where access to therapeutic abortions is restricted or not available should consider not allowing the use of this medication at all, or at the very least applying vigorous restrictions to its use (Garcia-Bournissen, 2008:127). The safe management of the teratoginicity effect of isotretinoin is very important to ensure that this highly effective drug stays on the market to serve as a cure for patients suffering from severe acne.

2.4.5.3 Liver and blood effects

Blood tests to determine baseline liver enzyme levels and triglycerides need to be done before treatment starts and should be repeated after one month of treatment. Should the baseline and one-month values both be normal, further blood testing is unnecessary (Sinclair & Jordaan, 2005:889-890).

In a study done on South African acne patients, who were taking isotretinoin, ±5% experienced abnormal liver function tests and a mean overall change in cholesterol readings showed a rise of 10.5%, this usually returned back to normal after therapy (Smart & Walters, 1994:500).

In a study done by Baxter *et al.* (2003:218), they came to the conclusion that there appeared to be no adverse trends in serum cholesterol or triglyceride profiles following large cumulative doses, including patients who had been using isotretinoin for three courses or more in an acne population. This indicates that even if isotretinoin is used for long periods it does not affect cholesterol and triglycerides in a harmful way after therapy has been completed. However, triglyceride levels rise more dramatically during the first 8 weeks of therapy but stabilise thereafter (Baxter *et al.*, 2003:217).

It is important not to donate blood while on isotretinoin treatment and for one month after discontinuation of treatment. If someone who is pregnant receives donated blood containing isotretinoin, her baby may be exposed to isotretinoin and may be born with birth defects (FDA, 2005).

2.4.5.4 Depression

Consensus has not been reached on the issue of depression and suicide resulting from the use of isotretinoin. Because of the background prevalence of depressive symptoms in patients with acne, it is difficult to distinguish between drug-related and non-drug-related depressive symptoms, such as environmental or physiologically induced symptoms. In addition there is no known biologic mechanism of action to support such a causal relationship (Hersom *et al.,* 2003:425). Two comprehensive reviews have recently focused on this issue of isotretinoin and the link to depression (Jacobs *et al.*, 2001:198; Ng and Schweitzer, 2003:78) and concluded: "...causal relationship between isotretinoin therapy and depression has not been clearly established...".

In the most recent study conducted by Gupta and Gupta (2008:AB2), they evaluated 9.6 million patient visits involving isotretinoin use, and their findings indicate that the lack of an association between isotretinoin and suicide in the large database (representing 10 years of patient visits, 1993 to 2003) further suggests that suicidal behaviour with isotretinoin represents an uncommon idiosyncratic phenomenon. In another study done in Australia they also came to the conclusion that there was no difference in the level of depressive symptoms in isotretinoin users compared to antibiotic/topical users (Ng *et al.*, 2002:266).

Less well known is the risk of this lipid-soluble chemical to affect the central nervous system. Reports of intracranial hypertension, depression, and suicidal ideation with isotretinoin use have prompted an examination of its serious and life-threatening potential. Although Roche® company has added a warning to its product label for signs of depression and suicidal ideation, this product is over-prescribed for all forms of acne, including mild and moderate cases that have not been treated with alternative medications with lower risk of depression and suicide (O'Donnell, 2003:148).

Isotretinoin (marketed as Accutane® in the USA) still ranks among the top 10 of the US Food and Drug Administration's database of drugs associated with reports of depression and suicide attempts. However, this association is still controversial because up to 5.6% of patients with moderate acne may have pre-existing suicidal ideations, improvement of acne often reduces associated depression, and isotretinoin users are reportedly no more likely than those taking antibiotics for acne to have depression or to commit suicide (Barak *et al.,* 2005:39).

From the initial marketing of isotretinoin in 1982 to August 2004, there were 4,992 spontaneous reports of psychiatric disturbances submitted to the FDA associated with using of isotretinoin in patients in the United States and the number of reported suicides among

isotretinoin users was 190 up to January 2005. Between 1982 and 2002, there were 165 reported suicides, which were fewer than the 220 predicted based on USA vital statistics data (FDA, 2005). However, because the degree of under-reporting of suicides is unknown, the fact that the reported number is lower than the predicted number cannot be interpreted as evidence against a causal association (FDA, 2005).

Although the controversy regarding a potential association between isotretinoin use and depression or suicidal behaviour in acne vulgaris patients remains a popular issue in the public media, the more rigorous scientific studies to date that have examined this proposed relationship have not identified such an association (Marqueling & Zane, 2005:101). Until compelling evidence on this issue is produced, continued vigilance is warranted for symptoms and signs of psychiatric disturbance among acne patients before, during and after isotretinoin therapy (Marqueling & Zane, 2005:101). The South African Guideline for Acne, still suggests that caution is advised in patients with a history of depression and that mood swings should be reported by the patient and the drug should be discontinued should any symptoms of depression occur on treatment (Sinclair & Jordaan, 2005:889).

2.4.5.5 Unusual adverse events/effects

For most of these unusual adverse events many studies should still be done to prove the validity of them being a side effect of isotretinoin.

The effect of oral retinoids on the bone are known, although it is only likely to happen in some cases, mostly when patients are on long-term treatment. These effects include retinoid hyperostosis, which is age-dependent, and premature epiphyseal closure, which happens very rarely in children and also only when high doses of isotretinoin are used in long-term treatment (DiGiovanna, 2001:S181). In a recent study done by DiGiovanna *et al.* (2004:716) it was proved that a single course (4-5months) of isotretinoin had no effect on bone mineral density in the age group of 12 to 17 years, proving the safe use of the drug as acne treatment in cases of bone mineral density dysfunctions.

In another unusual case a patient with severe nodulocystic acne developed disabling muscle stiffness and painful superimposed spasms of the neck, back and upper limbs 10 days after the onset of oral isotretinoin treatment. The muscle hyperactivity condition, which revealed the clinical and electromyographic features of the stiff-person syndrome, gradually resolved 2 weeks after drug withdrawal (Chroni *et al.*, 2002:886). Isotretinoin does cause muscle aches

and pains in about 20% of patients (Mclane, 2001:S193) and sometimes it can develop into more serious effects, although this very seldom happens.

In a recent study done by Aydogan and Karli (2006:84) it was suggested that isotretinoin might be capable of causing peripheral nerve-conduction abnormalities and in their opinion, investigations should be performed in all patients reporting symptoms of paresthesia, numbness, sensory loss before and during oral isotretinoin treatment.

Some usual side-effects, which are unusual for isotretinoin users, e.g. nausea, diarrhoea, and abdominal pain, are also rarely reported, but there are case reports of pancreatitis happening while on isotretinoin therapy (Greene, 2006:992; Katsambas & Papakonstantinou, 2004:415). Although there have been a few unidentified/unusual side-effects over the past 25 years the use of isotretinoin is still monitored very closely and any dangerous unusual adverse events should be identified easily and action should be taken accordingly.

2.4.6 Recurrence

The drug is administered for a period of time (typically 4 to 6 months) and then is withdrawn, yet often the beneficial effects continue for a few months afterwards, but still recurrences/relapses of acne may occur in up to one quarter (20-25%) of patients, although the relapsing acne is equally responsive to repeated courses of isotretinoin therapy (Ellis & Kent, 2001:S156; Wessels *et al.*, 1999:784).

However, studies show recurrence more frequently happening in patients who

- are under 16-years old;
- receive low-dose-therapy (0.1–0.5 mg/kg) and not reaching the cumulative dose of 120mg per kg;
- suffer from truncal acne;
- presented with patients with sinus drainage disease or lesions with hemorrhagic crusts;
- patients with adrenal or ovarian syndrome; and
- show high androgen levels (Leyden, 1997:29; Thielitz *et al.*, 2006:277; Janson & Plewig, 1997:321-334).

There is no correlation between recurrence and the patient's gender, treatment duration (if 120 mg/kg is still reached), or the severity of the acne (White *et al.*, 1998:378). While sebum suppression can occur at relatively low doses of isotretinoin, long term remissions of acne are more closely correlated with the cumulative dose and duration. It appears from years of collected experience that cumulative dose may be more important than the total duration of therapy (Hirsch & Shalita, 2001:162). Most important, a total dose of less than 120mg/kg of body weight is found to have a higher rate of relapse (Haryati & Jacinto, 2005:1000) and also an increasing total cumulative dose are related to lower relapse rates (Ng & Goh, 1999:216).

In about 10% of cases of recurrence experienced, the acne is severe enough to require a second course of isotretinoin (Sadick, 2002:90). The beginning of maintenance therapy with a topical retinoid after discontinuation of oral isotretinoin may help prevent relapses by controlling microcomedone formation and to improve scarring (Thielitz *et al.*, 2006:277).

A recent study done by Azoulay *et al.* (2007:1240) on a large population indicated a higher percentage of 41% of subjects experiencing an acne relapse and 26% required a second isotretinoin treatment course. These are relatively high percentages and recurrence in isotretinoin usage should be looked at and managed accordingly. But still the most important aspect is that isotretinoin should be prescribed in the correct dosage to prevent recurrence of acne.

2.4.7 Drug interactions

It is important that patients inform the health care professional about all the medicines they are taking, including prescription and non-prescription medicines, vitamins, and herbal supplements, because not all drug interactions with isotretinoin are clearly known.

Known drug interactions include the following:

- Vitamin A, Acitretin, tretinoin (systemic) - Additive toxicity (Hypervitaminosis A) with concurrent use. Vitamin A-containing nutritional supplements should be avoided (Isotretinoin is a vitamin A-analog).

- Tetracycline medicines - Concomitant use should be avoided. Both agents have been associated with benign intracranial hypertension.

- Alcohol – both influence changes in the liver enzymes and lower the efficacy of isotretinoin. Alcohol intake should be lowered or rather stopped.

- Cyclosporine and azole antifungals (e.g. ketoconazole and itraconazole)- isotretinon induces hepatic and cutaneous microsomal P-450 enzymes and these drugs may be affected by it.

- Dilantin (phenytoin), Corticosteroid medicines, St. John's Wort – these drugs should be used with caution.

- Progestin-only containing birth control pills ("minipills") – this contraception could fail. (FDA, 2005; Gibbon *et al.*, 2005:194; Hanson & Leacman, 2001:177)

Other interactions include: The concurrent use of 'peeling agents', such as sulphur, benzoyl peroxide and salicylic acid, is not recommended. The skin should be rested until effects of these agents subside before introducing topical retinoids. Similar precautions apply to the use of medicated or abrasive cleaners, soaps, degreasing agents and cosmetics that have strong drying effect (Gibbon *et al.*, 2005:194).

2.5 EFFECT OF ISOTRETINOIN ON THE QUALITY OF LIFE

Clinical experience suggests that most of the quality of life effects of acne are predominantly confined to a period between 15 and 30 years of age. Certainly severe scarring acne does affect some individuals past the age of 30, so this assumption may underestimate the impact of acne on quality of life and, therefore, underestimates the benefit of isotretinoin in the treatment of acne (Jordan *et al.*, 2005:191).

The Quality-adjusted life years (QALY) benefit of treating patients with severe acne is 50 times greater than the risk of QALY loss from isotretinoin teratogenicity in this population; for patients with moderate and mild acne the QALY benefit is 11 and 7 times greater, respectively. When assuming an 85% probability of success with treatment, the benefit of isotretinoin use in severe, moderate, or mild acne appears quantitatively greater than the risk of teratogenicity or any other side-effects (Jordan *et al.*, 2005:191).

Acne has a considerable impact on quality of life, especially for severely affected individuals (Hanna *et al.,* 2003:8) and thus the potential benefit from isotretinoin treatment is so great that removing it from the market would cause more harm than good (Jordan *et al.*, 2005:191-192).

2.6 ISOTRETINOIN GEL

The topical form of isotretinoin (Isotrex®) is in a gel format. Although systemic isotretinoin is very effective the topical agent does not compare in its effectiveness, because the working mechanism is reduced to only the reduction of comedos (microcomedos) and inflammation and does not cover all of the same pathologic factors of systemic treatment (Gollnick *et al.*, 2003:S5).

The effectiveness of topical isotretinoin in comparison to other topical retinoids does not differ on a large scale (refer to section 2.3.6.2). The results of a study indicate that both adapalene and isotretinoin gels were highly effective in treating facial acne, although adapalene gel produced greater reductions in non-inflammatory and inflammatory lesion counts than isotretinoin gel, during the 12-week period of once-daily application. The differences in reduction between treatments were not significant at the end of the study, but adapalene gel was significantly better tolerated than isotretinoin gel during the whole treatment period (Io Annides *et al.*, 2002:526). Thus it would be more sensible to prescribe adapalene than topical isotretinoin in order to minimise side-effects and maximise compliance.

2.7 ASPECTS OF ISOTRETINOIN USAGE IN THE LITERATURE

There are on average 6.2 million visits per year to office-based physicians (in the United States) where acne is listed as a reason for the visit or as a physician diagnosis (Stern, 2000:1045). This again emphasises the importance of acne to the general public and although it is not life-threatening it is life-altering. Because of this, effective acne drugs are on high demand by everyone who wants a cure for acne. A similar situation is present in South Africa.

The goal of the National Drug Policy is to ensure an adequate and reliable supply of safe, cost-effective medicines of acceptable quality to all citizens of South Africa and the rational use of medicines by prescribers, dispensers and consumers (Department of Health, 1996).

With the rapid increase of isotretinoin usage shown by Wysowski *et al.*, (2002:505) with an increase of 2.5-fold (250%) from 1992 to 2000, the importance of the drug is growing rapidly, and note that this increase took place before the introduction of generics in 2002. Even though these statistics do not apply to South Africa, it is more than likely that the same would have happened in South Africa. Furthermore, Wysowski *et al.* (2002:505) also showed a decline in treatment of severe acne with isotretinoin and an increase in the proportion of

treatment for mild and moderate acne with isotretinoin. A study done by Thevarajah *et al.* (2005:225) on the American population of doctors over a 13-year period from 1990 to 2002, indicated significant declines in the likelihood of prescribing all antimicrobial products, whereas there were significant increases in the likelihood of prescribing topical and systemic retinoid (isotretinoin) agents. All of these studies emphasised the growing popularity of this effective acne drug.

2.7.1 Gender difference

In a study done in the United States between 1994 to 1999 on the prescribing of isotretinoin, it was found that the sex distribution was nearly even, 48% of prescriptions were for males and 50% for females (2% were unspecified). These nearly equal sex ratios have been consistent over the period (Wysowski *et al.*, 2002:507). A recent study done by Asoulay *et al.* (2006:670) also indicated that the gender difference was very small and isotretinoin was similarly prescribed to males and females, at 50.2% versus 49.8%, respectively.

A relatively similar tendency was found in a South African study where Wessels *et al.* (1999:787) had a large study group for patients using systemic isotretinoin which consisted of 45% males and 55% females, which reflected the gender distribution of South Africans using isotretinoin.

We could expect that isotretinoin would be prescribed predominately to male patients, because of the teratogenicity effect which only applies to the female patients. Even so, women account for almost 65% of visits for acne as a principal diagnosis or reason for visit to registered prescribers (Stern, 2000:1045; Fleischer *et al.,* 2003:664). Although per capita acne visits were higher for women, men were 1.7 times more likely than women to receive isotretinoin during an acne visit. Isotretinoin was prescribed during 13% of women's acne visits and 22% of men's acne visits (Fleischer *et al.,* 2003:664). Together with this men were found less likely to receive clindamycin and topical retinoids and more likely to receive tetracycline group antibiotics and oral isotretinoin (Thevarajah *et al.*, 2005:225).

More notable is the difference in the age distribution between men and women who seek care for acne. The majority of women seeking care for acne are 20 years of age or older. In contrast, more than two thirds of male persons who seek a physician's care for acne are younger than 20 years. For every visit by a man older than 20 years, there were nearly 4 visits by women in this age group, suggesting that many women past teenage years perceive acne as a continuing problem that is sufficiently severe to warrant medical attention (Stern,

2000:1047). The concern however in gender difference is the high number of female patients using systemic isotretinoin, in spite of the severe teratogenicity effect of the drug.

2.7.1.1 Female exposure to isotretinoin being a problem

The use of contraception is compulsory for women of child-bearing age (12 years and older) and who have a sexually active lifestyle, while at the same time receiving isotretinoin treatment. Although the guidelines recommend the use of two different contraceptive methods (Sinclair & Jordaan, 2005:889), a study done by Smart and Walters (1994:501) in South Africa, indicated that more than half the women participating in the study did not use any form of contraception as it was deemed unnecessary. This group included patients who were not sexually active, had given informed consent or had religious objections to contraception. Pregnancies do occur in spite of precautionary measures.

In a recent study done by Bèrard *et al.* (2007:200), in Canada, of the 8 609 women that were included in this cohort, 210 were pregnant at any given point in time during their isotretinoin regimen: 68 (32%) had already been pregnant by the time they started their first isotretinoin prescription, 90 (43%) became pregnant while taking isotretinoin and 52 (25%) became pregnant within 1 month of isotretinoin discontinuation. These statistics indicate a high prevalence of over 2% (four times greater than any other study) of the female patients of child-bearing age becoming pregnant. Similar guidelines as are currently being used in South Africa had also been at the disposal of the prescribers and females who fell pregnant. Whether they adhered to the guidelines has no been stated.

Another study indicated that women who enrolled between 1989 and 1999, women between the ages of 25 and 35 years, had the highest pregnancy rate (3.7 pregnancies per 1000 courses of isotretinoin). This compares with a rate of 2.8 pregnancies per 1000 isotretinoin courses in women between the ages of 15 to 24 years. Pregnancies occurred in all age groups, but the rates were lower among women under 15 and over 34. The pregnancy rates per 1000 courses of isotretinoin for ages < 15 years, 35 to 44 years, and > 45 years were 1.0, 1.7, and 0.5, respectively (Goldsmith *et al.*, 2004:903). These statistics of confirmed pregnancies indicate the need for strict programmes and emphasise the crucial importance of following all the guidelines very precisely for as long as isotretinoin treatment lasts and for at least one month after discontinuation.

Furthermore only 34% of women had received anti-acne medications other than isotretinoin before their first isotretinoin prescription, even though the majority had been treated by

dermatologists (Bèrard *et al.,* 2007:200). In South Africa, Wessels *et al.* (1999:789) found that only 16.8% of female isotretinoin users were co-prescribed oral contraceptives, but there are no documented studies on the occurrence of pregnancies while on isotretinoin in South Africa.

As long as isotretinoin is marketed, a certain degree of contraception failure, either by failure of contraceptive means or by failed compliance, will most probably continue to occur (Garcia-Bournissen *et al.,* 2008:127) and we do not know whether the problem of the occurrence of unwanted pregnancies would be solved.

2.7.2 Age difference

In a study done in South Africa on the age-by-gender distribution of the systemic isotretinoin treated patients, 56.5% were aged 20 years and older, and 25.4% were 30 years or older. The median female age was 25 years, while the median age for males was 19 years (Wessels *et al.,* 1999:787). The results of this study seem to indicate that isotretinoin usage is becoming more prevalent among older patients, but another study done by Wysowski *et al.* (2002:507) showed that a total of 63% of males who had been prescribed isotretinoin were 15 to 19 years old, whereas 51 % of females were 15 to 24 years.

In a comparative study, patients of all ages were treated and the age group 10 to 19-years had about 60% of isotretinoin visits. The visits decreased continuously with age in patients 20 years and older (Fleischer *et al.,* 2003:663). Teenagers can be considered the group most frequently affected by *acne vulgaris* and they were also most frequently prescribed isotretinoin, but still a significant proportion (40%) of treatments occur beyond the teenage years and into the third and fourth decades (Fleischer *et al.*, 2003:665).

From 1995 to 1998, both the number of prescriptions of isotretinoin dispensed and the number of visits with isotretinoin prescribed were equal for men and women. Men aged 19 years and younger accounted for more than two thirds of all visits where isotretinoin was prescribed, but more than 70% of women to whom isotretinoin was prescribed were 20 years of age and older. In addition, physicians may reserve this therapy for older women, whom they may believe to be more likely to adhere to a Pregnancy Prevention Programme (Stern, 2000:1047).

Females were on average 4.5 years older than males when they received isotretinoin, they were more often living in urban settings as compared to males, and consulted physicians more often than males in the 12 months prior to receiving isotretinoin. Females were also

2.7.4 Drugs prescribed in combination with isotretinoin

In 91% of cases, isotretinoin was prescribed as monotherapy with no other medicine combined on the same prescription. Combinations that did occur were with topical clindamamycin, doxycycline, minocycline, prednisone, and topical tretinoin (Wysowski *et al.*, 2002:507). Some studies also indicated that there were few prescriptions where there could be potential drug-drug interactions with the drugs prescribed together with isotretinoin, especially systemic tetracyclines (including minocycline) and vitamin A (Smart & Walters, 1994:499).

An analysis of drugs co-prescribed with systemic isotretinoin done in South Africa indicated that there was a relatively low incidence of co-prescribing. The most frequently co-prescribed drugs were the oral contraceptives. However only 14.4% of females receiving isotretinoin treatment were also using these agents. Of these 12.2% were using the cyproterone/oestrogen combination also used for acne treatment. If child-bearing age is defined as between the ages of 13 and 45 years, then 16.8% of eligible female patients appeared to be using oral contraceptives. All the other agents included medicines like erythromycin, benzoyl peroxide, sulfamethoxazole/trimethoprim, minocycline e.g. were co-prescribed at a frequency of less than 1.5% (Wessels *et al.*, 1999:788).

A study done by Hersom *et al.* (2003:429-430) indicated a high number of patients using anti-depressants together with isotretinoin, at almost 15% of isotretinoin users, but for the study purpose only about 0.97 % first used isotretinoin then received antidepressant therapy in addition. This corresponds with control cases of minocycline and antidepressant treatment on the same basis (0.98%). This study indicated no association between depression and isotretinoin usage (Hersom *et al.*, 2003:431). The problem here is that although isotretinoin may not cause depression, there is still a guideline implemented, indicating that isotretinoin should not be prescribed if any depression symptoms occur, let alone, being prescribed to those who are already using antidepressants. More caution should be taken when prescribing isotretinoin together with antidepressants and when depression occurs while patients are using isotretinoin. If these scenarios occur the drug use should be stopped (Gibbon *et al.*, 2005:194).

2.7.5 Dosage variations

The optimum dosage and some different dosage variations have been reviewed in section 2.4.4. In this section the observations are related to dosage variations. The focus is on what

taking fewer anti-acne medications other than isotretinoin than males ($p<0.05$) (Azoulay *et al.,* 2006:670).

All of these studies found in the litrature indicated which age groups have the highest prevalence of isotretinoin users and they also indicated that female patients were usually older than male patients when they received isotretinoin. On another aspect the European directive decided isotretinoin would no longer be recommended for children under 12 years (Thielitz *et al.,* 2006:276). This has not yet been incorporated in South Africa. There are no guidelines for using isotretinoin in the elderly.

2.7.3 Prescribing by medical practitioners

Nearly 90% of US prescribers, prescribing isotretinoin, were dermatologists and only about 8% were general practitioners (Wysowski *et al.*, 2002:507). A similar study confirmed that dermatologists prescribed isotretinoin more frequently than did any other specialty and accounted for more than 80% of isotretinoin visits. There were at least 80-fold more isotretinoin visits per year to dermatologists than to any other medical specialists (Fleischer *et al.*, 2003:664; Stern, 2000:1048; Goldsmith *et al.*, 2004:903).

Because of the high demand for such professionals, the waiting time to consult a dermatologist could be several weeks. As such, non-dermatologists, especially general practitioners, become the best alternative. In such cases where more dermatologists are required the majority of prescriptions for isotretinoin at index date were written by physicians at 76.8% of prescriptions (Azoulay *et al.*, 2006:670).

Although dermatologists have been using isotretinoin for indications other than acne for a long time now, there are still no other new approved indications for isotretinoin. Dermatologists compared with non-dermatologists were more likely to use isotretinoin, clindamycin, topical retinoids and tetracycline group antibiotics for the treatment of acne (Thevarajah *et al.*, 2005:226; Doering *et al.,* 1992:160).

In the early nineties the dermatologists in the USA believed they should have sole authority for prescribing isotretinoin (Doelring *et al.*, 1992:160), a pattern integrated in Australia and in some European countries (see table 2.6, section 2.4.5.2). In spite of this, in the US, among the women who had isotretinoin exposed pregnancies, the highest proportion (approximately 85%) received their isotretinoin prescriptions from dermatologists (Goldsmith *et al.*, 2004:903).

could be successful in future and implemented in SA or, for that matter, across the world. In the study done by Wysowski *et al.* (2002:508), in the United States, the 40mg level was the most prescribed formulation with 78% of mentions, followed by 14% for 20mg and 4% for 10mg. The 40mg formulation is not available in South Africa, only the 20mg and 10mg strengths.

Dosing of 1 mg/kg for 4 to 5 months resulted in the lowest rate of relapse, and that dose became the standard recommendation (Leyden, 1998:S45). The dosing regimen may be variable, but international consensus suggests that a total dosage of 120 mg/kg is necessary for full effect of the drug, and that no additional benefit can be expected from a cumulated dose of more than 150 mg/kg. The total cumulative dose appears to be a better predictive factor than clinical response when risk of relapse is assessed. The survey suggests that both parameters are used in practice since 61% of the respondents use clinical effect and 56% use total cumulated dose (Wildfang *et al.*, 2002:151).

Six months of treatment with low-dose isotretinoin (20 mg/d) was found to be effective in the treatment of moderate acne, with a low incidence of severe side-effects and at a lower cost than higher doses (Amichai *et al.,* 2006:644). This could be a reason why some dermatologists prescribe low-dose isotretinoin, but still isotretinoin is not indicated for moderate acne and the identified dose range for successful treatment is higher.

In a study done on medium dose isotretinoin for the treatment of moderate to severe acne, the mean daily isotretinoin dose was close to 30 mg or 0.43 mg/kg body weight, with a mean duration of treatment slightly exceeding 8 months. It had a relapse rate of 33%, which is slightly on the high side and although the success rate is relatively good in excess of 60% (Herms *et al.*, 1998:118-119), it is not satisfactory. The normal recommended regimes have a lower percentage of relapses and better success rates.

In a study done by Akman *et al.* (2007:473) they also tested the use of a intermittent dosage regimens (taking 20mg (0.5mg/kg) for the first 10 days of every month for 6 months) in mild acne and found that it was very effective with fewer side-effects, but they indicated that although it was effective it had a higher rate of relapses than the normal dose, probably because the cumulative dose had not been reached. Further studies on intermittent dose regimens for isotretinoin must be done.

In a study done by Smart and Walters (1994:499) on the different aspects of isotretinoin prescription in South Africa it was found that the mean daily dosage prescribed at initiation of therapy was 0.64 mg/kg. Initial daily doses prescribed ranged from 0.12 mg/kg to 1.33 mg/kg; the median dosage prescribed was 0.63 mg/kg and the SD 0.24. Marked differences

were evident in the mean dosages prescribed by general practitioners and dermatologists, with general practitioners prescribing a mean starting dose of 0.36 mg/kg/day and dermatologists a mean starting dose of 0.68mg/kg/day. Similar differences were evident in the dosage prescribed at follow-up visits (Smart & Walters, 1994:499).

As said before one of the earliest noted complications of acne treatment with oral isotretinoin was an explosive flare of inflammatory lesions and the subsequent development of crusted, ulcerated lesions, frequently with exuberant granulation tissue. This usually happens when isotretinoin is started at high dose regimens. It should now be routine practice to initiate treatment at doses no higher than 0.5 mg/kg and frequently even lower, gradually increasing the dose if the severity or locations of the lesion so warrant it (Hirsch & Shalita, 2001:163). Some medical doctors used an interesting new regime; they begin dosing at 10 to 20 mg/day and slowly titrate to the next step of 40 mg/day and only then, if tolerated, titrating them to the final dose of 1 mg/kg/day (Hirsch & Shalita, 2001:164).

2.7.6 Generic prescribing

Generic brands are less expensive than the innovator products and the lower cost has the potential to increase the number of individuals using a drug. Lower cost can also encourage more prescriptions for a drug earlier in the course of treatment of the given condition. In the case of isotretinoin, availability of generics might lead to greater use as a first-line drug for less severe cases of acne.

The expiry of the patent exclusivity to Roche® pharmaceuticals opened a lucrative market and at the end of 2002 when the new generic products of systemic isotretinoin were introduced into world markets (Koren *et al.*, 2004:1567). Health insurance plans usually encourage the prescribing of generics, which might make physicians more likely to write a prescription for a generic drug now that generics for this drug are available and coverage by a health insurance plan will remove a potential barrier. Patients may also be more prepared to fill a prescription (Honein *et al.*, 2004:1075). All generic versions combined usually account for half of the prescriptions dispensed by 1 to 3 years after they have entered the market, with the first generic to enter the market having the greatest share (Suh *et al.*, 2000:529). By the end of the first 12 months that generic isotretinoin had been available, the three generic brands available in the USA, combined had approximately 60% of the total market share. Roche® net US sales for their original systemic isotretinoin product (Accutane®) fell from $US380 million in 2002 to $US144 million in 2003 (FDA, 2004).

There are over 30 names under which isotretinoin is sold worldwide, including at least 25 generics and generic brands. Both the names and prices of isotretinoin vary dramatically between countries (Honein *et al.*, 2004:1076). As discussed earlier, any increase in isotretinoin use would be expected to result in an increased number of pregnancies exposed to isotretinoin (Honein *et al.*, 2004:1075).

The use of generic isotretinoin may be affected by a study done on the differences of generic isotretinoin versus the original (Roaccutane®) by Taylor and Keenan (2006:603) on fourteen generic isotretinoin products. They compared these products on different bases. The 14 isotretinoin products differed by 30-fold in median particle size and showed variation in their non-active ingredients. The average isotretinoin content of two of the generics fell outside the 95-105% Roche® specifications. Thirteen generic products failed to match Roaccutane® in one or more tests and 11 failed in three or more tests. Therefore it cannot be assumed that all generic isotretinoin products are as therapeutically effective or safe as Roaccutane® (Taylor & Keenan, 2006:603). None of the different generics of isotretinoin that had been tested included one of the generic products available in South African.

2.7.7 Influences on isotretinoin prescribing

The first and most important influence when prescribing isotretinoin is the teratogenic effect of the drug and caution should be taken when isotretinoin is prescribed to female patients of child-bearing age (discussed in sections 3.2.1 and 2.4.5.2). Another important aspect is drug interactions (refer to section 2.4.7). Most of the reasons for influences in isotretinoin prescribing have been mentioned in previous sections except for some of the special prescribing points and other reasons in prescribing isotretinoin, which should be taken into account when isotretinoin is prescribed or dispensed.

The South African Medicines Formulary (Gibbon *et al.*, 2005:194-195) has a long list of special prescribing points that should be taken into consideration when systemic isotretinoin is prescribed. It includes the following:

- Obesity, diabetes mellitus, alcohol consumption and a family history of hyperlipidaemia are risk factors for the development of raised plasma lipids.
- Special investigations during therapy should include serum lipids and liver function (before and after 1 month of therapy, relative to risks), blood glucose, haematology and uric acid (as indicated).

- Depression is a perceived complication of acne. This may be exacerbated by isotretinoin. Psychological evaluation of acne patients is an important aspect of acne management. Depression should be identified and managed appropriately.
- Exacerbation of acne may be seen initially.
- Exposure to excess ultraviolet radiation (including sunlight) should be avoided.
- Patients are advised not to donate blood while taking isotretinoin (or for 1 month after discontinuation) since recipients may be exposed to the toxic and teratogenic effects.
- The patient should be given oral and written warnings of the dangers of pregnancy.
- Limit concurrent vitamin A intake, including health foods, diet and over-the-counter preparations.
- Uncontrolled headaches need investigation to exclude raised intracranial pressure.
- Regular use of lip preparations and emollients controls cheilitis and dry skin.
- Dryness of the eyes may cause intolerance to contact lenses.
- Owing to temporary difficulties in dark adaptation, problems may be experienced with night driving.
- Musculoskeletal pain may be aggravated by excessive exercise.

All of these points do not necessarily influence the prescribing of isotretinoin but many of these points are not mentioned or explained to the patient either by the prescriber (dermatologists, general practitioners, etc.) or the provider (Pharmacies, dispensing doctors, etc.).

Some countries implemented managing programmes to prevent adverse events (especially teratogenic effects). The USA introduced the iPLEDGE programme (mentioned in section 2.4.5.2) and the Europeans formed the European Directive for prescribing systemic isotretinoin for acne vulgaris. This European Directive includes a pregnancy prevention programme and certain recommendations outlined in table 2.7.

Table 2.7: Summary of the recommendations (Layton *et al.*, 2006:774)

	Pre-European Directive	Post-European Directive
Dosage recommendations	Between 0.5 mg/kg and 1mg/kg	Treatment to start at 0.5 mg/kg
Acne severity	Isotretinoin was previously recommended as first-line therapy for severe acne (nodular, conglobata) as well as acne not responding to at least 3 months of systemic antibiotics combined with topical therapy.	The new recommendations suggest isotretinoin should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy (it should not be used as first-line therapy).
Age limit	Previously no age limit.	Not recommended in children under 12 years of age.
Monitoring	Liver enzymes and lipids should be checked before treatment.	Check before and 1 month after starting treatment and every 3 months thereafter.

A study by Mendelsohn *et al.* (2005:615) indicated a decrease of isotretinoin prescriptions after a regulating programme had been introduced. The decrease was approximately 23% in the year following the newly introduced regulating programme. In contrast a study done by Azoulay *et al.* (2006:671) indicated that no significant impact was seen on the number of new isotretinoin users when new guidelines were introduced. Regulating programmes do not necessarily need to decrease the use of isotretinoin, they should only ensure that guidelines are correctly followed and that adverse effects are kept to the minimum or totally eliminated.

The influence of skin colour on the prescribing of retinoids is not known, together with the limited studies on the effect of retinoids on skin of colour. A study done by Jacyk (2001:42) found that retinoids (including isotretinoin) proved to be an effective well-tolerated therapy for black patients and for this reason there should not be an influence in the prescribing of isotretinoin to patients of different colour.

The high cost of isotretinoin treatment is also a major influence in prescribing, especially in patients without a medical aid (refer to section 2.7.8).

Despite receiving the information and reporting confidence in medication knowledge, patients' understanding of major risks with these medications was poor. This finding highlights the need to develop better risk communication strategies to improve the safe and effective use of prescription medications (Allen LaPointe *et al.*, 2007:98).

2.7.8 Cost of acne medication and isotretinoin

Knowing that acne is the most common dermatological condition, it could be expected to also have the biggest impact on dermatological costs. Clearly acne is a substantial problem, which causes patients to initiate millions of visits per year to physicians and with a total cost of acne likely to exceed $1 billion annually in the USA (Stern, 2000:1048). Patients suffering from acne will be making an ever-increasing demand on health care resources (Wessels *et al.*, 1999:780). At an average annual drug cost of R2 670 per patient for the treatment of acne and an average incidence of 2.7% of beneficiaries, medical schemes are faced with a conservatively estimated drug bill of R7.2 million per 100 000 beneficiaries (Wessels *et al.*, 1999:790)

A decade ago dermatological products in South Africa made up 6-7% of the reimbursed pharmaceutical benefits bill in 1997, showing an increase over the 1996 percentage of 5-6%. While it is very difficult at present to get accurate data on diseases in South Africa, approximately 55% of the money reimbursed for dermatological products is attributed to acne. In terms of specific drugs used in acne treatment, isotretinoin attracts the biggest reimbursement (Wessels *et al.*, 1999:780).

Thevavajah *et al.* (2005:227) came to the conclusion that the economic forces (private health care sector) of the population helped to dictate prescribing behaviour for isotretinoin prescriptions, since the private heath sector is the only force that is generally capable of paying for this expensive drug. The study done by Wessels *et al.* (1999:785), indicated an annual pharmacotherapy expense per patient on isotretinoin of R6 140. Even though isotretinoin is cost-effective (Wessels *et al.,* 1999:794) and generics are available on the market (at first the generic product was only 5.5% lower in cost in relation to the original product (Skernivitz, 2002:1)), the cost is still very high in relation to other acne products, e.g. benzoyl peroxide.

A specific treatment cost could not be specifically identified since the dosage differs for every individual patient and the cost of isotretinoin differed much over the last few years, especially when the generics were introduced. A study done by Moore (2006:122), indicated that the average cost of medicine products containing isotretinoin claimed was R999 ± 661 in 2001 (before the introduction of generics) and R 425 ± 401 in 2004 (after the introduction of generics and the single exit price) in the months of May to August for each year. The indirect costs are not taken into account in this study, but if we take these extra costs of isotretinoin into consideration, e.g. doctor's visits, blood test, contraception, pregnancy tests, moisturisers, etc., the cost of this already expensive isotretinoin treatment regimen will

continue to increase. From all of the above it would appear that acne, and especially isotretinoin treatment, will continue to be a major expense to the funders of health care.

2.8 MANAGED HEALTHCARE

There are different definitions for managed healthcare: The definition of managed healthcare by Cohen (2003:34) suggested that managed healthcare would include any kind of healthcare service which are paid for, all or in part by a third party, including any government entity and for which the focus of any part of clinical decision making is other than between the practitioner and the client or patient.

Managed healthcare attempts to create an organised system where care that is medically necessary is delivered by properly trained and educated healthcare professionals, in appropriate locations and facilities and under practice guidelines that are likely to produce results for patients (Shoaf, 1999:242).

The Council of Medical Schemes (Medical Schemes, 2003) recognises the potential advantage of managed healthcare to the extent that it can achieve the following:

- Encourage the use of most cost-effective health care delivery mechanisms, and thus accomplish cost reduction.
- Align the financial incentives of providers and financiers to reduce bad incentives for unnecessary care.
- Establish mechanisms to maintain or improve quality of care.
- Promote the development of standardised treatment plans.
- Support patients in gaining access to the most suitable treatment interventions.
- Promote an integrated approach to managing the health care needs of patients (Medical Schemes, 2003).

Another aspect in the management of health, appropriate for this study, is disease management. According to Labiris (2003:168) disease management is the systematic, population-based approach to identify people's risk, intervene with specific programmes of care and measure clinical and other outcomes.

Three primary elements of disease management include the following:

- Knowledge base that quantifies the economic structure of the disease and describes guidelines for discrete patient segments.
- A delivery system of health care professionals and organisations closely coordinating to provide care throughout the course of a disease.
- A continuous improvement process that measures clinical behaviour, refines treatment standards and improves the quality of care provided (Tremonti, 1998).

The South African perspective of managed healthcare suggests that managed healthcare means an arrangement by means of which utilisation of healthcare is monitored through the use of mechanisms, which are designed to monitor appropriateness, promote efficacy, quality and cost-effectiveness of the delivery of relevant health services (Managed Health Care Systems, 2006)

2.8.1 Drug utilisation review

In the previous decade Guo *et al.* (1995:1175) defined a drug utilisation review (DUR) as an authorised, structured and continuing programme that reviews, analyses and interprets patterns of drug usage in a given health care system against predetermined standards. The principal aim of drug utilisation is to facilitate rational use of drugs in the population. For the individual patient rational use of a drug implies the prescription of a well-documented drug in an optimal dose according to the appropriate indication, with the correct information and at an affordable price (Sjöqvist & Birkett, 2003:78). Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better. Drug utilisation research in itself does not necessarily provide answers, but it contributes to rational drug use. One of its components includes drug use evaluations.

The objectives of drug use evaluation include the following:

- Ensuring that drug therapy evaluation meets current standards of care
- Controlling drug cost
- Preventing medication-related problems

- Evaluating the effectiveness of drug therapy
- Identification of areas of practice that require further education (Sjöqvist & Birkett, 2003:81)

By participating in a drug utilisation evaluation programme one can improve quality of care for patients, individually and as a population, by preventing the unnecessary or inappropriate drug therapy and preventing adverse drug reactions (US Pharmacopeia Drug Utilization Review Advisory Panel, 2000; Weber, 1999).

The types of drug utilisation studies:

- Cross-sectional studies – these data provide a 'snapshot' of drug use at a particular time
- Longitudinal studies – study the trends of drug use (it can be on a total drug use as obtained from a claims database)
- Continuous longitudinal studies – usually at a practitioner where the individual is unique and drug prescription can be followed (WHO, 2003:17)

Important to this study is retrospective drug utilisation. A retrospective DUR study evaluates data on drug prescribing; dispensing and/or patient use after the drug has been dispensed, in a given health care environment against predetermined agreed upon criteria and standards (Blackburn *et al.*, 2001:7).

A retrospective review may detect patterns in prescribing, dispensing, or administering of drugs to prevent recurrence of inappropriate use or abuse and serves as a means for developing prospective standards and target interventions. In retrospective DUR, patient medical charts or computerised records are screened to determine whether the drug therapy met approved criteria. These medical charts or records aid prescribers in approving care for their patients, individually and within groups of patients, such as those with specific chronic diseases (Weber, 1999:2).

There is an interest in shifting retrospective DUR to include disease management concepts and this will help improve the effectiveness and efficiency of pharmacists' health care interventions (US Pharmacopeia Drug Utilization Review Advisory Panel, 2000).

The other types of DUR include: Prospective drug utilisation – this study evaluates individualised or aggregated data on drug prescribing and/or dispensing prior to prescribing,

in a given health care environment, against predetermined, and agreed upon criteria and standards (Blackburn *et al.,* 2007:7). Concurrent drug utilisation – this study evaluates drug dispensing, prescribing and/or patient use at a point in time or intervals through acute or ongoing therapy and includes a timeframe from the onset (Blackburn *et al.,* 2001:8).

The goal of the DUR programme is to emphasise the patient's safety by an increased review and awareness of prescribed drugs (Owens, 2005). The overall cost of drugs must be reduced; as well as patient care that must be improved (Idaho State University, 2005).

According to Weber (1999:3-4) the following five steps are essential when conducting any quality-related drug utilisation evaluation programme:

- Identify or determine optimal use
- Measure actual use
- Compare
- Intervene
- Evaluate the drug utilisation programme.

2.8.2 Pharmacoepidemiology

Pharmacoepidemiology is defined as the study of the use and effects or side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs and improving health outcomes (Sjöqvist & Birkett, 2003:77). Strom (2005:4) also stated that pharmacoepidemiology is the study, the use of and the effects of drugs in large numbers of people; focusing on a specific field, which is primarily concerned with studies of adverse drug effects.

Pharmacoepidemiology currently focuses on pharmaceutical care outcomes and the identification of potential or realised drug use problems (Waning & Montagne, 2001:4). The basic idea is to measure the source, diffusion, use, and effects of drugs in a population and to determine the frequency and distribution of drug use outcomes in that population. More specifically it is performed to

- describe current problems of drug use in a specific population;
- determine changes in drug use over time;

- measure the effects of information, education, promotional activities, media accounts and price of drug use;
- detect inappropriate drug use associated problems;
- estimate drug needs in terms of disease patterns and outbreaks; and
- plan the selection and distribution of drugs (Waning & Montagne, 2001:5).

2.8.3 Pharmacoeconomics

Health economics aims to define the cost and benefits of medical interventions, in such a way as to support decisions about whether health services should invest in particular activities (Walley, 1999:S3). The economical aspects of medical interventions are becoming more important because of the health care expenditures that are increasing dramatically. This is why there is a worldwide recognition of the need to control the rising cost of healthcare (Ellis *et al.*, 2002:271; Jessop *et al.*, 2002;568).

Pharmacoeconomics includes the description and analysis of the cost of drug therapy to a health care system and society. It identifies, measures and compares the cost and consequences of pharmacoeconomical products and services (Bootman *et al.*, 1991:4).

The common types of studies in pharmacoeconomics include these 5 related types of economic evaluation analyses in healthcare:

- Cost-minimisation analysis – This compares the cost of interventions that yield the same results, and is done with the intention of identifying the intervention that has the lowest cost (Ellis *et al.*, 2002:274; WHO, 2003:26). This method is used to compare generic and innovator drugs that have shown to be equivalent in dose and therapeutic effect (WHO, 2003:26).

- Cost-effectiveness analysis – This is when the cost and consequences are simultaneously measured; effectiveness in terms of obtaining a specified objective and cost in monetary terms (Bootman *et al.*, 1991:4). When a treatment is more effective but also more expensive, cost-effectiveness analysis helps quantify the clinical and economic consequences of using it (Ellis *et al.*, 2002:274). This method is often used to examine alternative therapies for a single disease. The incremental cost-effectiveness ratio refers to the amount of money needed to produce an additional benefit (Ellis *et al.*, 2002:275).

- Cost-benefit analysis – This is when cost and consequences are simultaneously measured in terms of money units. It improves the decision-making process in allocation of funds to health care and other programmes (Bootman *et al.*, 1991:5). This method is used to attempt to overcome the inability to compare various results by translating outcomes into money units and then for making resource allocation decision across health care fields or across economic sectors (Ellis *et al.*, 2002:278).

- Cost-utility analysis – This is focused on the consequences and are measured in terms of quality of life, willingness to pay or preference of one intervention to another (Bootman *et al.*, 1991:4; WHO. 2003:27). This method is similar to cost-effectiveness analysis except that it incorporates a measure of quality into the outcomes of the interventions under study (Ellis *et al.*, 2002:276; WHO, 2003:27).

- Cost-of-illness analysis – This evaluation identifies and evaluates the direct and indirect cost of a particular disease (Bootman *et al.*, 1991:5). This method is used to calculate the sum of medical resources used to treat the specific illness (hospital care, professional services, drugs and supplies); the non-medical resources associated with it (transport, lodging for the family during treatment and employing a person to help with home care); and the loss of productivity due to illness or disability (indirect cost) (Struwig, 2001:60).

The focus of the present study is on the prescribing patterns and cost of isotretinoin products. The more specific objectives are stated in chapter 3.

2.9 GOALS OF HEALTHCARE

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human-being without distinction of race, religion, political belief, economic or social condition (WHO, 2006).

The dictionary definition for health care is the prevention, treatment, and management of illness and the preservation of mental and physical well-being through the services offered by the medical and allied health professions (The free dictionary, 2008).

The mission of the South African Department of Health is to improve access to health care for all and reducing inequity, and to focus on working in partnership with other stakeholders to improve the quality of care of all levels of the health system, especially preventive and

promotive health, and to improve the overall efficiency of the health care delivery system (Department of Health, 2008).

Each year 8% or more of the gross national product (GNP is an indicator of the wealth produced by the country) is spent on the national health system, including both the public and private health sectors. On average 60% of this is spent in the private sector, which provides care to 20% of the population. The remaining 80% of the population relies on the public health system for health care. This sector receives 40% of total expenditure on health. Any national policy must therefore include both private and public sector issues, and by so doing, contributing towards strengthening the partnership between the public and private sectors. (Department of Health, 2007)

Isotretinoin products evaluated in this study falls under the private health care sector of South Africa.

If we want to reach the goal of the National Drug Policy to ensure an adequate and reliable supply of safe, cost-effective medicines of acceptable quality to all citizens of South Africa and the rational use of medicines by prescribers, dispensers and consumers (Department of Health, 1996), I believe studies of this kind are very important.

2.10 CHAPTER SUMMARY

In this chapter an overview of the skin anatomy was given with reference to the pilosebaceous unit, the site of origin in acne. Acne was discussed together with the different treatments. The major focus was, however, on isotretinoin. The known aspects of isotretinoin were discussed through available literature, giving bases to what this study could be compared to. The relevant managed health care aspects for this study were reviewed. Lastly the goal of health care was stated. The next chapter contains the method of this empirical study.

CHAPTER 3

EMPIRICAL INVESTIGATION

In this chapter both the general and specific research objectives of the research project as well as the research methodology of this empirical investigation will be described. The procedures followed in acquiring the relevant information and the subsequent analysis of the data will also be discussed.

3.1 RESEARCH OBJECTIVES

The research objectives are divided into a general objective and specific objectives.

3.1.1 General objective

The general objective of this study was to investigate the prescribing patterns, including aspects of cost, of isotretinoin products in a section of the private health care sector of South Africa, according to a pharmacy benefit management company, including different comparisons of isotretinoin products. The data available on the medicine claims database, received from the pharmacy benefit management company, were divided into the two study years of 2005 and 2006.

3.1.2 Specific objectives

This research project consists of two phases, namely a literature review and an empirical investigation.

The research objectives of the two phases include the following:

Phase 1: Literature objectives

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

- To present a brief overview of the anatomy of the skin, with reference to the pilosebaceous unit.
- To review acne as a disease and the treatments available.
- To present an overview (including indications, dosages, adverse effects and interactions) of isotretinoin treatment through available literature.
- To investigate different aspects (including age, gender and prescribers) of isotretinoin treatment through available literature.
- To mention briefly what managed health care, including drug utilisation review, pharmacoepidemiology and pharmacoeconomics, consist of.

Phase 2: Empirical objectives

The specific research objectives of the empirical study were the following:

- To determine the prescribing patterns including aspects of cost of isotretinoin products, with comparison to acne products and the total claimed medicine items in a section of the private healthcare sector of South Africa.
- To determine the cost and prevalence difference between the innovator and the generic isotretinoin products.
- To identify the differences in prescribing patterns of isotretinoin between the major medical prescribers of isotretinoin.
- To identify age group differences in the prescribing patterns of isotretinoin.
- To determine and identify the difference in the prescribing patterns of isotretinoin in the different genders.

- To identify combination therapy with isotretinoin products and determine any possible concerns.

3.2 RESEARCH METHODOLOGY

The objective of the study was to review, analyse and interpret prescribing patterns including the cost associated with isotretinoin products, together with comparing it to the total acne products identified and/or the total products available on the database. The prescribing patterns were determined after the drug had been dispensed and paid for by the pharmacy benefit management company.

The research methodology included the literature study and the empirical study.

3.2.1 Literature study

A literature study was done with regard to relevant literature from journals, textbooks and other sources, including the internet.

The literature study consisted of a review divided into two parts. The first part was a brief overview of the skin and acne which included the anatomy of the skin (with reference to the pilosebaceous unit), acne epidemiology, pathogenesis, acne grading, acne scarring, quality of life in acne and acne therapies. This part also included an overview of isotretinoin and included the clinical effects of isotretinoin, effect of isotretinoin on the quality of life and the topical form of isotretinoin.

The second part consisted of the gathering of information on the aspects of isotretinoin usage available in the literature and focused on the same aspects that are evaluated in this study, *i.e.* gender, age, prescriber, co-prescribed drugs, dose variations, generic prescribing and cost. In this part a description of managed health care concepts relevant to this study is also included.

3.2.2 Empirical study

A retrospective drug utilisation study was done on isotretinoin products claimed through a medicine claims database of a pharmacy benefit management company for the years 2005 and 2006. Other data obtained also included the total acne products identified and the total data of all the medicine claims on the database for the same study period. The medicine claims database included approximately 34% of the total number of beneficiaries in the private heathcare sector of South Africa. The statistical analysis of the data was done with the SAS 9.1.® Computer package (SAS institute Inc, 2004). The years 2005 and 2006 were chosen in order to obtain the most recent data available and no major cost or prevalence influences occurred over the two study years.

The following steps were included in the empirical investigation:

- Data source and the study population – with reference to the occurrence and the quantity of data evaluated.

- Research design and selection of research instruments – which are the backbone of this study and outline what have been selected to be studied. The focus of the study was the isotretinoin products described in chapter 4. The research instruments included all the listed instruments in paragraph 3.6.

- Analysis of data – data analysis and manipulation were done by statistical methods. Statistical concepts were utilised to analyse the data according to the measuring instruments.

- Reliability and validity – the data were extracted directly from the medicine claims database and are believed to be correct and precise.

- Results and discussion are based on findings in the empirical study. These will be discussed in chapter 4.

- Conclusions and recommendations are based on the results of the empirical investigation. These will be outlined in chapter 5 (including limitations).

3.3 DATA SOURCE

The data were retrospectively obtained from the medical claims database, with the permission of the pharmacy benefit management company. Data were obtained over a period of two years (1 January 2005 to 31 December 2006). The two study years offered the most recent electronic data available for the study, which included 12 months data per year.

Each medicine item contained an unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the pharmacy benefit management company, providing the data, to ensure confidentiality. Thus confidentiality of information was maintained throughout the study (also refer to section 3.8). The database contained information such as:

- medical scheme member number (numbers were randomised for privacy);
- dependant number;
- prescription number;
- date of dispensing of the prescription;
- trade name of the medicine item;
- NAPPI code of the medicine item;
- quantity of the medicine items prescribed;
- days supplies;
- generic indicator;
- member date of birth (age was calculated on the day the medicine was claimed);
- member gender;
- the prescriber;
- the provider; and
- the cost per medicine item (including total cost, final scheme amount and final levy; only total cost was used).

3.4 STUDY POPULATION

The study population for both study years (1 January 2005 to 31 December 2006) consisted of all the data available on the database. This included a total number of 17 569 799 prescriptions, containing a total number of 41 333 753 medicine items with a total cost of R3 940 321 304 (refer table 4.1 and table 4.3.1). From these data the number of isotretinoin containing prescriptions was identified.

3.5 DATA ANALYSIS

The statistical analysis system, SAS (SAS institute Inc, 2006) was used to analyse the data. The analysis consisted of three parts. The fist part of the analysis was performed on all medicine items and the second part of the analysis was performed on the acne products identified on the database. The focus was, however, on the third part of the analysis, *i.e.* specifically on the isotretinoin products available on the database.

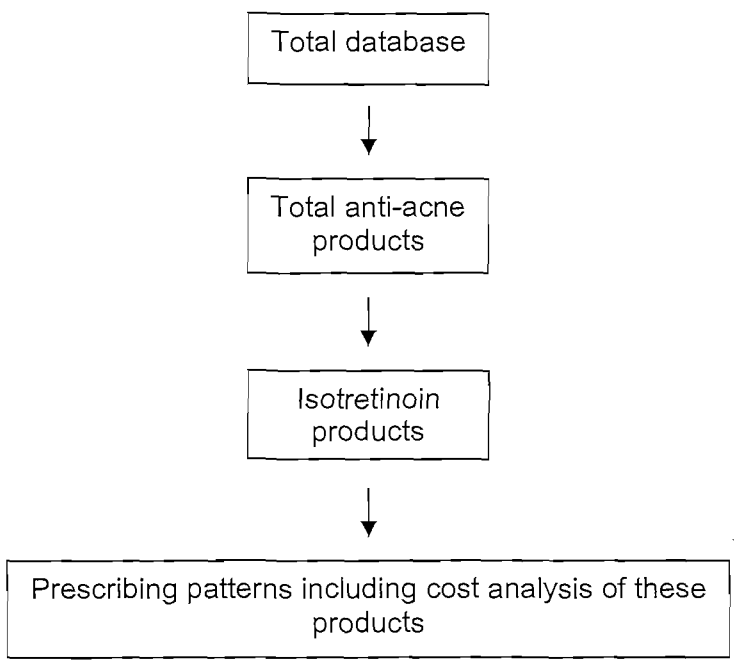

Figure 3.1. Pathway of the analysis followed to extract the data.

3.5.1 Classification systems

Various classification systems were used to classify medicine claimed through the database such as the Monthly Index of Medical Specialities (MIMS®) classification and the NAPPI code.

3.5.1.1 MIMS classification

According to the MIMS® classification (Snyman, 2005:237), isotretinoin products are classified under acne medication, which is again classified under dermatological products. The identified acne products were classified according to the MIMS® classification, including only the acne medicine classified in section 14.6 of the MIMS® classification system.

3.5.1.2 The NAPPI code

The NAPPI (National Pharmaceatical Product Interface) code is a unique nine-digit number implemented with electronic transactions in mind. Any given ethical, surgical and consumable product can be uniquely identified by the NAPPI code. This code is unique for each product name, pack size, strength, manufacturer plus exclusions (Snyman, 2005:7a). For the purpose of this study the specific isotretinoin products and specific acne products on the database were identified by means of their specific NAPPI codes.

3.5.2 Statistical analysis

The following descriptive statistical concepts were utilised to analyse the data according to the measuring instruments / criteria as discussed in section 3.6.

3.5.2.1 Average value (mean)

The average that uses the exact value of each entry is the mean (it can also be called the arithmetic mean) (Brase & Brase, 1999:94). The mean value is the best known single numerical value used to indicate the central position / location of the numbers (Steyn *et al.*, 1994:90). To compute the mean, the sum of all values making up the set of observations, is divided by the total number of observations in the set (Benerjee, 2003:3).

The equation is as follows:

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

$\bar{x}$ = the mean

$\sum$ = the sum of

n = number of observations

x = value in the data set

3.5.2.2 Standard deviation

The standard deviation is defined by Banerjee (2003: 5) as a measure of the spread of data about the mean, weighting each individual item by its distance from the centre of the distribution. The standard deviation is a good descriptive measure of variability, although it can be affected strongly by outliers (Cohen & Lea, 2004:15).

The equation is as follows:

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

s = standard deviation

x = value in the data set

$\bar{x}$ = arithmetic mean

n = number of observations

3.5.2.3 Cost-prevalence index

The cost-prevalence index indicates the relationship between the total number of medicine items prescribed or claimed and the total medicine cost (Serfontein, 1989:181). The cost-prevalence index can be defined / computed as follows (Serfontein, 1989:180):

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

For the purpose of this study the cost-prevalence index was used at times during data analysis to determine the expensiveness of a product relative to the number of medicine items prescribed.

Cost-prevalence values were interpreted as follows (Serfontein, 1989:180):

- Cost index < 1: Consumed treatment is relatively inexpensive.
- Cost index = 1: The cost of treatment is symmetric to the prevalence.
- Cost index > 1: Consumed treatment is relatively expensive.

3.5.2.4 Effect sizes (d-values)

Cohen (1988:9) defined the effect size (*d*) as the "*degree with which the phenomenon is present in the population*". Effect size is an indication of the number of standard deviations where two population means are apart (Cohen & Lea, 2004:125). In this study the effect size will be used to determine whether there is any practical significant difference between the different prescribed average medicine treatment costs.

The effect size can be calculated by the following formula (Steyn, 1999:3):

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

d = effect size

$\overline{x_a}$ = average medicine treatment value of a

$\overline{x_b}$ = average medicine treatment value of b

s_{max} = the maximum standard deviation between treatment value a or b

The d-value can be interpreted as follows (Steyn, 1999:3):

$d = 0.2$ small effect. (These results are regarded as insignificant.)

$d = 0.5$ medium effect which is observable and may be significant.

$d = 0.8$ large effect which is significant and of high practical importance.

$d > 0.8$ assumed to have practical significant value.

3.6 MEASURING INSTRUMENTS

In attaining the objectives set out in this study, the following measuring instruments or criteria were selected for use:

- Medicine items
- Cost
- Gender
- Combination
- Prevalence / Frequency
- Age groups
- Prescriber

3.6.1 Medicine items

Medicine items are defined according to the Medicines and Related Substances Control Act (101/1965) as "substance intended for use in the diagnoses, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man". In this research the words "medicine items" is used interchangeably with the word "drugs". Medicine items are used in this study as a research instrument, to identify different prescribing patterns through claims of the number of medicine items dispensed, including the average number of medicine items per prescription, indicated for the total database, the acne medicine items and the isotretinoin medicine items.

Prescriptions claimed were identified according to the medicine items a prescription contained, except for the total database where any prescription claimed was identified with no preference to the medicine item it contained. All prescriptions containing an isotretinoin medicine item were identified and used for analysis of the prescribing patterns of isotretinoin.

3.6.2 Prevalence / Frequency

Prevalence is the proportion of individuals in a population suffering from a disease. Prevalence is a statistical concept referring to the number of cases of a disease present in a particular population at a given time (Medicine Net, 2008). According to Waning and Montagne (2001:21) prevalence is defined as "the probability that a condition exists in a specific population or the probability of the occurrence of the condition".

Frequency is the number of items of which a particular value occurs in a set of data, or the number of times a particular category occurs (Martin & Pierce, 1999:13). The Merriam-Webster dictionary defines frequency as the number of times that a periodic function repeats the same sequence of values during a unit variation of the independent variable, which include the number, proportion, or percentage of items in a particular category in a set of data (Merriam-Webster, 2008a).

In this study, the prevalence / frequency of isotretinoin products will be analysed as follows:

- Prevalence of isotretinoin prescriptions and medicine items claimed during the study period.
- Prevalence of acne medications claimed during the study period.
- Prevalence according to generic and innovator isotretinoin products.

- Prevalence according to the specified age groups and different genders.
- Prevalence difference in prescribing between the prescribers of isotretinoin.
- Frequency of drug combinations with isotretinoin on the same prescription claim.
- Frequency of isotretinoin medicine items in relation to the identified acne medicine items and the medicine items on the total database.

Frequencies of the acne products identified are also included in the study.

3.6.3 Cost

Cost is defined by Vogenberg (2001:3) as the value of resources consumed. Larson (1996:46) defined medicine cost as the monetary value of resources consumed in the production or delivery of medicine. In this study cost was expressed as a rand-value (R).

The total medicine cost, the average medicine cost per prescription, the average medicine cost per item as well as the cost-prevalence index were analysed:

- The total cost of all medicine items claimed during the two study years were identified as for acne medicine and isotretinoin, these costs were then compared for 2005 and 2006.
- The cost differences between the generic and innovator isotretinoin products were compared.
- The cost differences between the isotretinoin products and the total anti-acne products were investigated.
- The cost differences between gender, age groups and prescribers of isotretinoin were analysed.
- The cost prevalence was analysed where it was deemed necessary.

3.6.4 Age groups

The Merriam-Webster dictionary describes age as the part of life from birth to a given time (Merriam-Webster, 2008b). The age of the patient in this study was determined according to the date of birth of the patient and the date of the prescription, thus the age of the patient was the specific age of the patient on the date that the prescription was dispensed.

In this study the age of the patients were divided in five age groups as follows:

- Age group one (1): >0 to ≤2 years
- Age group two (2): >12 to ≤9 years
- Age group three (3): >19 to ≤27 years
- Age group four (4): >27 to ≤35 years
- Age group five (5): >35 years

The age groups were identified according to the ages where the highest prevalence of acne cases occurs, identified as the ages between twelve and thirty-five years (refer to section 2.3.1). The age groups were evaluated on different bases (see chapter 4).

3.6.5 Gender

The World Health Organization (2007) defines the sex of an individual as the biological and physiological characteristics that define men and women; and gender as the socially constructed roles, behaviours, activities, and attributes that society considers appropriate for men and women. In other words male and female are sex categories and masculine and feminine are gender categories (World Health Organization, 2007). Sex thus refers to an individual's gender classification: male or female.

For the purpose of this study gender and sex will be seen as synonyms and will be used to indicate whether a prescription was prescribed and claimed for a male or a female patient. The prescribing patterns for isotretinoin products of the different genders were investigated and compared. The different genders and the identified age groups were combined and the prescribing patterns thereof were indicated.

3.6.6 Prescriber

The definition for prescriber is to give directions, either orally or in writing, for the preparation and administration of a remedy to be used in the treatment of a disease (The Free Dictionary, 2008). The prescriber is the person who prescribes and / or has the authority to prescribe medicine. This study only included the major contributors of prescribed isotretinoin products claimed through the database. The general medical practitioner and the dermatologist are the two prescribers investigated in this study, together with a group called the other prescribers which would include all the authorised medical prescribers excluding the two mentioned. The differences in their prescribing patterns of isotretinoin products and acne products were evaluated.

3.6.7 Combinations

Combinations refer to the medicine items prescribed and claimed together with isotretinoin medicine items on the same prescription. Only the most prevalent combinations were evaluated, to identify certain prescribing patterns of combined prescribing or interactions between isotretinoin and the combined medicine item. A drug interaction can be defined as an interaction between a drug and another substance that prevents the drug from performing as expected (Ogbru & Marks, 2003). Drug interactions were compiled from the literature, indicating all the different medicine products that may interact with isotretinoin therapy (See section 2.4.7 for isotretinoin drug interactions).

3.7 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENTS

The data for analysis were directly obtained from a medicine claims database. Direct manipulation of the data by the researcher was therefore impossible. The research was conducted under the impression that all data obtained from the database were precise and correct (refer to limitations in section 5.4). Data for analysis were obtained from one medicine claims database, thus limiting external validity, implying that results can be generalised to the specific database only, as well as the specific study population.

3.8 ETHICAL APPROVAL

Within the medicine claims database the individual patients and prescribers could not be identified and the study was concluded anonymously. Ethical approval was obtained at the North-West University (NWU-0046-08-S5).

3.9 DISCUSSION OF THE RESULTS OF THE EMPIRICAL INVESTIGATION

The discussion and results of the empirical study will be documented in Chapter 4.

3.10 CONCLUSION AND RECOMMENDATIONS

The conclusions and recommendations based on the results of the literature review and the empirical investigation will be discussed in Chapter 5.

3.11 CHAPTER SUMMARY

In this chapter the research methodology was explained. The discussion included both the general and the specific research objectives of the literature and the empirical investigation, data sources, study population, data analysis and measuring instruments. The next chapter (Chapter 4) contains the results of the empirical study.

CHAPTER 4

RESULTS AND DISCUSSION

In this chapter the results of the empirical investigation of the prescribing patterns and cost of isotretinoin containing products, the identified acne medications and the total meidicine claims database are discussed. The results pertain to the two study years from 1 January 2005 to 31 December 2006. In figure 4.1 is a layout of the chapter contents.

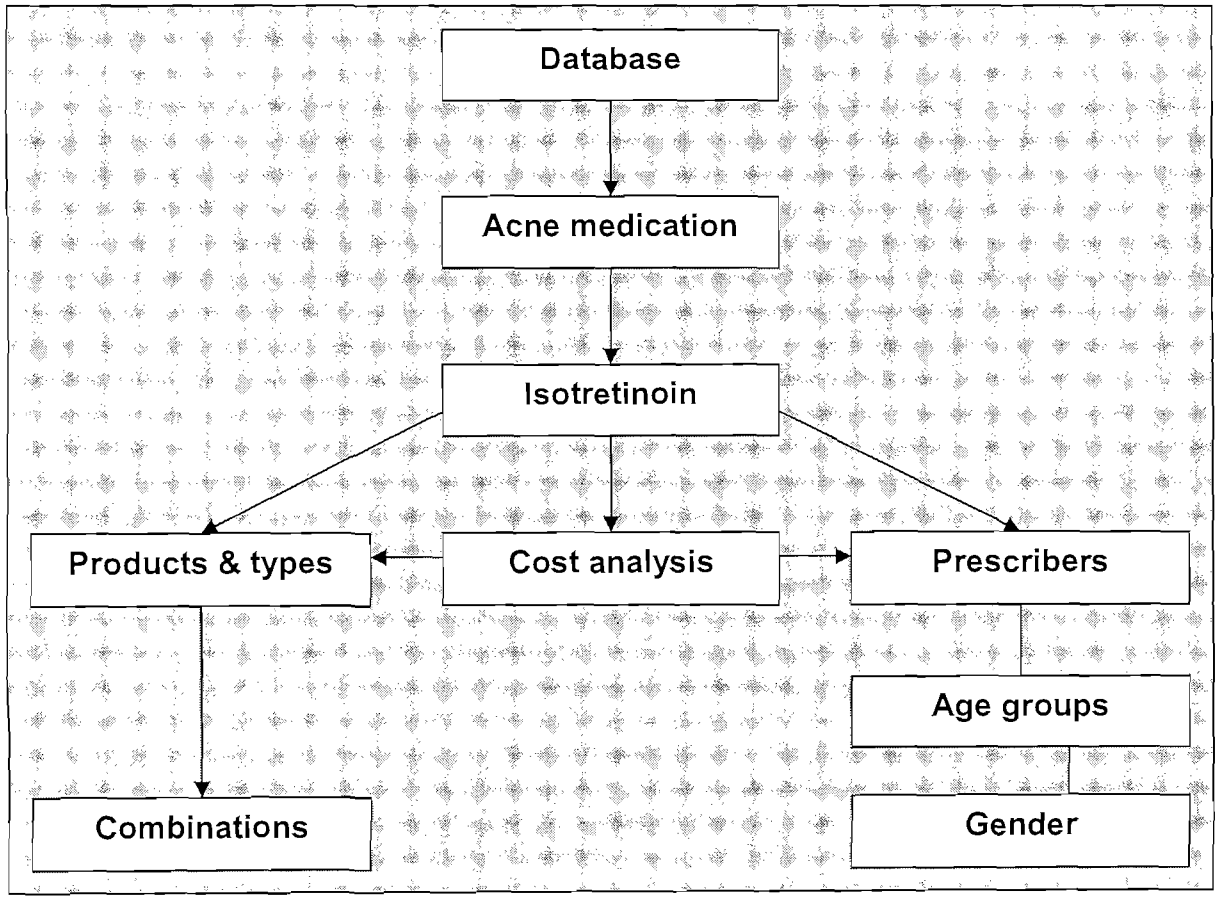

Figure 4.1: Layout of the prescribing patterns of isotretinoin containing products covered in this chapter.

4.1 CLARIFICATIONS WITH REGARD TO THE INTERPRETATION OF THE RESULTS

- For the purpose of this study, two one-year intervals were compared, the years 2005 and 2006. The intervals were as follows:
    - 1 January 2005 to 31 December 2005
    - 1 January 2006 to 31 December 2006
- The medicine products that are listed in this study are the medicine products that were claimed through the medicine claims database of a Pharmacy Benefit Management Company (PBM) and are restricted to medicine products that are available on the South African market.
- The percentages have been rounded off to one decimal, except when the percentage recorded was smaller than one, in such cases it was rounded off to two decimals. The averages and d-values were rounded off to two decimals.
- For calculations of percentage increase/decrease of the different average costs between study years, the standard deviation was not taken into consideration.
- Isotretinoin containing items, isotretinoin medicine items and isotretinoin items for the purpose of this study can be used interchangeably or as a synonym. Isotretinoin items refer to all of the different isotretinoin products available.
- Isotretinoin prescriptions and acne prescriptions refer to prescriptions where one of the medicine items on the prescription was an isotretinoin containing product or one of the identified acne products respectively.
- Acne products or anti-acne products for the purpose of this study can be used interchangeably or as a synonym. The acne/anti-acne products are products where the main indication for these products is for the condition referred to as acne. The MIMS® classification was used (refer to section 3.5.1.1).
- Innovator and original medicine for the purpose of this study is used interchangeably or as a synonym. The innovator/original drug refers to the first drug of this pharmacological nature that was introduced to the market.

- Generic medicine refers to a product where the patent of the innovator/original medicine had expired and other companies would have the right also to manufacture and market a product containing the same pharmacologically active ingredient.

- Non-generic refers to a product that does not have a generic substitute available on the market at the time of the study (e.g. the topical form of isotretinoin (Isotrex gel®) has no generic substitute available on the market in South Africa).

- Different types of medicine items, indicate the innovator medicine items, the generic medicine items and the non-generic medicine items.

- Different isotretinoin products, indicate the different dosage forms and the different marketing names under which isotretinoin is available in South Africa, this includes Roaccutane® 10mg and Roaccutane® 20mg (the innovator), Acnetane® (10mg and 20mg, generic), Oratane®(10mg and 20mg, generic) and Isotrex® Gel (the only topical form available during the study period).

- For the purpose of this study the terms general medical practitioners and general practitioners are used interchangeably or as a synonym.

- Due to ethical and protective reasons no specific prescriber or provider could be identified and therefore no specific trends of isotretinoin prescribing by certain practices and pharmacies could be identified. Only a reflection of what and how isotretinoin was claimed through this PMB could be identified for this study.

- Every time a prescription or a repeat prescription was claimed it counted as one prescription claimed through the PMB.

- All the indications and classifications of the different medicine items prescribed in combination with isotretinoin products were identified according to the MIMS® (Monthly Index of Medical Specialities by Snyman *ed.*, 2005:1-390) and the SAMF® (South African Medicines Formulary by Gibbon *ed.*, 2005:1-581).

- Database refers to the medicine claims database provided by a PBM for analytic purposes.

4.2 GENERAL MEDICINE PRESCRIBING PATTERNS

General medicine prescribing patterns include discussions on the total medicine items, the acne medication and the isotretinoin medicine available on the medical claims database.

Table 4.1: General prescribing patterns of the number of prescriptions and medicine items for the years 2005 and 2006 according to the medicine claims database.

	Year	Total number of prescriptions (N)	Percentage prescriptions (%)	Total number of medicine items (N)	Percentage medicine items (%)
Total database	**2005**	8 522 574	100	19 860 679	100
	2006	9 046 138	100	21 473 074	100
	Total	**17 568 712**		**41 333 753**	
Acne products	**2005**	111 618	1.3*	127 735	0.64*
	2006	107 832	1.2*	124 067	0.58*
	Total	**219 450**		**251 802**	
Isotretinoin products	**2005**	18 589	0.22* (16.7)**	21 632	0.11* (16.9)**
	2006	20 232	0.22* (18.8)**	23 532	0.11* (19.0)**
	Total	**38 821**		**45 164**	

*Percentage was calculated according to the total number of prescriptions or medicine items claimed on the total database for the specific year.

**Percentage was calculated according to the total number of acne prescriptions/medicine items claimed for the specific year.

4.2.1 General prescribing patterns of medicine items

The database consisted of a total number of 17 568 712 prescriptions claimed during the study period 1 January 2005 to 31 December 2006. The total number of prescriptions claimed increased by 6.1% from 2005 (n = 8 522 574) to 2006 (n = 9 046 138).

The total number of prescriptions contained a total number of 41 333 753 medicine items over the two-year study period. In comparison with the total number of prescriptions claimed for this period the total number of medicine items claimed increased by 8.1% from 2005 (n = 19 860 679) to 2006 (n = 21 473 074) (refer to table 4.1). This higher percentage increase in the total number of medicine items was possibly the result of a slight increase in the average

number of medicine items per prescription from 2.33 ± 1.56 to 2.37 ± 1.58 respectively for 2005 and 2006 (refer to table 4.2).

The average number of prescriptions per patient also indicated a relatively small increase from 6.98 ± 7.83 to 7.17 ± 8.05 prescriptions per patient respectively for 2005 and 2006 (refer to table 4.2). The d-value of 0.02 indicated that no major (practical significant) change occurred over the two study years.

The increases identified in both the number of prescriptions and the number of medicine items claimed during this study period may be due to an increase in the number of medical schemes that claimed through the PBM, a possible increase in the number of medical aid members and/or their dependants and the relatively small increase in the average number of prescriptions per patient over the two-year study period. These aspects are, however, outside the scope of this study.

The total number of prescriptions and medicine items shown on the database serve as a platform for this study to perform a retrospective analysis of the prescribing patterns of isotretinoin.

4.2.2 General prescribing patterns of acne medicine

A total number of 219 450 prescriptions containing acne medication were claimed over the two year study period (for acne medicine classifications refer to section 3.5.1.1). These acne prescriptions accounted for 1.3% (n = 111 618) and 1.2% (n = 107 832) of the total number of prescriptions claimed respectively for 2005 and 2006 (refer to table 4.1). This indicated a decrease of 3.4% in the number of acne prescriptions from 2005 to 2006 whilst the total number of medicine items claimed increased with 6.1% (refer to previous section 4.2.1).

In relation acne medicine items identified only accounted for 0.64% (n = 127 735) of the total number of medicine items claimed during 2005 and 0.58% (n = 124 067) during 2006 (refer to table 4.1). The total number of acne medicine items also indicated a decrease of 2.9% from 2005 to 2006. This decrease was very different from the 8.1% increase experienced in the total number of medicine items of the total database.

Reasons for the decrease in acne prescriptions and therefore also a decrease identified in acne medicine items claimed are unknown, but this could be due to possible changes with regard to medical schemes' payment for acne medicine, the influence of cost or an increase in the usage of other medicine items not included in the classification system followed by this

study (refer to limitations in section 5.4). It may also have been influenced by contracting more medical schemes with patients in the older age groups.

4.2.3 General prescribing patterns of isotretinoin products

A total number of 38 821 isotretinoin containing prescriptions were claimed over the two-year study period. The isotretinoin prescriptions represented 16.7% (n = 18 589) and 18.8% (n = 20 232) of all identified acne prescriptions claimed respectively for 2005 and 2006. In relation to the total number of prescriptions claimed on the database, isotretinoin prescriptions only represented 0.22% of prescriptions claimed for both 2005 and 2006 (refer to table 4.1).

The total number of isotretinoin containing prescriptions increased by 8.8% from 2005 (n = 18 589) to 2006 (n = 20 232). This increase was higher in relation to the 6.1% increase in the total number of prescriptions on the database.

The total number of isotretinoin items represented 16.9% (n = 21 632) and 19.0% (n = 23 532) of all acne medicine items claimed respectively for 2005 and 2006 and represented only 0.11% of the total number of medicine items in both 2005 and 2006 (refer to table 4.1). The difference in the number of isotretinoin items and the number of isotretinoin prescriptions was due to combinations of the different isotretinoin dosage forms (10mg and 20mg capsules) available prescribed together to achieve the desired daily dose (refer to section 4.5.3).

Even though there was an increase in the total number of isotretinoin items over the study period the total number of acne medicine items, of which isotretinoin products is a part, still showed a decrease of 3.4%. The increase of isotretinoin medicine items and isotretinoin prescriptions was similar at 8.8% over the study period. Possible reasons for this increase may include:

- Increase in membership, especially in younger age groups
- Patient pressure applied on prescribers to prescribe isotretinoin
- A possible increasing marketing effect by providers
- Change in prescribing patterns for the indication of isotretinoin use from severe acne to mild and moderate acne
- Preference by prescribers
- Isotretinoin is becoming more affordable (refer to section 4.4)

However, the higer percentage increase of isotretinoin prescriptions and items in relation to the database should indicate that there is an increase in the usage of isotretinoin in this section of the private health care sector of South Africa.

The isotretinoin items per prescription were relatively constant at an average of 1.16 medicine items per prescription (refer table 4.2). This only includes combinations of the different dosage forms available for isotretinoin items and does not include other medicine items prescribed in combination with isotretinoin (medicine items prescribed in combination with isotretinoin will be discussed in section 4.10).

There are only two different strengths available for systemic isotretinoin in South Africa (the 10mg and 20mg capsules) in relation to three strengths available in the USA (including a 40mg capsule, refer to section 2.7.5). A topical form of isotretinoin is also available locally.

Table 4.2: The average number of prescriptions and medicine items per prescription for 2005 and 2006.

	The total database		Isotretinoin products	
	2005	**2006**	**2005**	**2006**
Average number of prescriptions per patient	6.98 ± 7.83	7.17 ± 8.05	2.89 ± 2.17	2.92 ± 2.15
Average number of medicine items per prescription	2.33 ± 1.56	2.37 ± 1.58	1.16 ± 0.39	1.16 ± 0.38

The isotretinoin products indicated an average number of 2.89 ± 2.17 and 2.92 ± 2.15 prescriptions per patient per year respectively for 2005 and 2006 (refer to table 4.2). These average numbers indicated an expected treatment period between 23 and 151 days (1 to 5 months). The literature treatment guidelines indicate that a treatment course should be between 4 to 6 months (Strauss *et al.*, 2007:656; Amichai *et al.*, 2006:644; Sinclair & Jordaan, 2005:890; Gollnick *et al.*, 2003:S29; Gibbon *et al.*, 2005:195, refer to section 2.4.4); this indicates that the results of the average number of prescriptions per possible treatment was relatively lower in relation to these guidelines. The reason for this occurrence could be that some patients claimed the first part of their isotretinoin course in the previous year or the treatment course went over into the following year and therefore not all prescriptions could be counted for a specific patient. This lower average number of prescriptions per patient could also be influenced by cases where the patient's medical aid fund was exhausted and the rest of isotretinoin prescriptions would not be reimbursed and were therefore paid in cash.

Only 25.4% (2005) and 25.9% (2006) of patients claimed 4 to 6 prescriptions of isotretinoin, which is the indicated treatment period. Where 67.4% (for 2005) and 67.2% (for 2006) claimed 3 or fewer prescriptions, it could have been influenced by the reasons stated in the previous paragraph or could also be due to side-effects where the treatment regimen was discontinued. There were 7.3% (2005) and 6.9% (2006) of patients claiming 7 or more prescriptions. Reasons may include patients that were on a longer treatment regimen or experienced recurrence of acne and went on a second course of isotretinoin treatment. (Refer to appendix A, table A1.1).

Making provision for this phenomenon, it is possible that the average treatment period could increase. This aspect was not further investigated as the standard deviation for both years indicated a maximum treatment period of 5.0 prescriptions claimed for both years, which fell within the indicated treatment period of 4 to 6 months.

The 2 508 (2005) and 2 588 (2006) patients that only claimed a single isotretinoin prescription could be a concern (refer to appendix A, table A1.1), especially if this indicated the misuse of isotretinoin for only a treatment period of one month. This, however, fell outside the scope of this study.

4.2.4 Number of patients

The number of patients that claimed through the database for the specific study years was identified at a total number of

- 1 218 358 (for 2005)
- 1 259 099 (for 2006)

patients (beneficiaries) claiming through this database. This indicated an increase of 3.3% in the total number of patients.

The total number of patients that claimed isotretinoin was also identified with a total number of

- 6 427 (for 2005)
- 6 927 (for 2006)

patients claiming their isotretinoin prescriptions (also indicated in appendix A, table A1.1). This indicated an increase of 7.8% in the number of isotretinoin users, which is a higher percentage increase in relation to the total number of patients, supporting the results of an increased use of isotretinoin in this section of the private heathcare sector of South Africa.

4.3 COST ANALYSIS

Table 4.3.1: *Cost analysis of all medicine items for 2005 and 2006*

Year	Average cost per prescription (R)	Total cost of all medicine items (R)	Percentage (%)
2005	222.16 ± 463.13	1 893 376 921	100
2006	226.28 ± 557.49	2 046 944 383	100

Table 4.3.2: Cost analysis of acne products for 2005 and 2006

Year	Average cost per acne prescription (R)	Total cost of all acne medicine items (R)	Percentage (%)*
2005	177.27 ± 146.99	19 786 957	1.05
2006	166.70 ± 139.77	17 975 540	0.88

*Percentage was calculated according to total cost of all medicine items claimed during the specific year.

Table 4.3.3: Cost analysis of isotretinoin products for 2005 and 2006

Year	Average cost per isotretinoin prescription (R)	Total cost for all isotretinoin items (R)	Percentage (%)*
2005	366.35 ± 223.52	6 810 090	34.4 (0.36)**
2006	322.92 ± 209.02	6 533 241	36.3 (0.32)**

*Percentage was calculated according to total cost of all acne medicine items claimed during the specific year.

**Percentage in brackets was calculated according to the total cost of all medicine items claimed during the specific year.

4.3.1 Average cost per prescription

The average cost per prescription of the total number of prescriptions claimed was R222.16 ± 463.13 and R226.28 ± 557.49 respectively for 2005 and 2006 (refer table 4.3.1). A relatively small increase in the average cost per prescriptions was seen over the two-year study period (d-value of 0.01).

In comparison the average cost of an isotretinoin prescription was R366.35 ± 223.52 and R322.92 ± 209.02 respectively for the years 2005 and 2006 (refer table 4.3.3) (the cost of medicine items occurring (and claimed) on the same prescription in combination with the isotretinion products were not taken into account when the average cost per isotretinoin prescription was calculated).

The average cost per isotretinoin prescription indicated a decrease of 11.9% (R43.43) over the two study years (d-value of 0.19, a practically insignificant decrease). In comparison a study done by Moore (2006:122) indicated an average cost of R999 ± 661 in 2001 (before the introduction of generics) and R425 ± 401 in 2004 (after the introduction of generics in 2002 and the introduction of the single exit price in 2004) for isotretinoin products, with a d-value of 0.87 indicating a practical significant decrease in the average cost (refer to section 2.7.8). This indicated a continued decrease in the average cost of isotretinoin over the past years, between 2001 and 2004 (identified by Moore) to the decrease identified in 2005 to 2006 indicated in this study. Possible reasons for this occurrence of a decrease in average cost from 2005 to 2006 could be the increased use of the generic products of isotretinoin (refer to section 4.4.1) and/or a decrease in isotretinoin cost overall.

The relatively high standard deviation seen in the average cost per isotretinoin prescription indicates the relatively large variance in prescription cost for each patient. The reasons for this occurrence could be that a prescribed daily dose recommended to be between 0.5 to 1mg/kg/day (refer to section 2.4.4) indicated that a big variance of daily dose existed between different patients and therefore the relatively large variance in prescriptions cost.

An estimated total treatment cost per treatment course of isotretinoin was calculated, if the treatment regimen of 4 to 6 months (Gollnick *et al.,* 2003:S29, refer to section 2.4.4) had been followed and the average cost per prescription had been used. The estimated cost per treatment course was between R1 465 and R2 200 in the year 2005 and between R1 290 and R1 940 for the year 2006. This is an estimated cost based on the average cost per isotretinoin prescription and this estimated cost per treatment course could differ by a much larger cost if generic cost difference, topical or systemic isotretinoin cost difference, daily dose per patient and other usage factors were taken into account.

4.3.2 Total cost

The total cost of all medicine items claimed through the database increased by 8.1% over the study period and the amounts were R1 893 376 921 and R2 046 944 383 respectively for the study years of 2005 and 2006 (refer to table 4.3.1). Acne products only represented 1.05% (R19 786 957) in 2005 and 0.88% (R17 975 540) in 2006 of the total cost of all medicine items claimed (refer to table 4.3.2) and reimbursed.

Isotretinoin total costs contributed 34.4% (R6 810 090) and 36.3% (R6 533 241) of the total acne medicine costs for 2005 and 2006 respectively. Isotretinoin represented the highest percentage of total costs in relation to any other acne product identified in both study years (refer to appendix A, table A1.2). This is an indication that isotretinoin treatment played the biggest role in acne medicine costs in relation to any other single acne medicine treatment identified.

Overall isotretinoin total costs only represented 0.36% and 0.32% of the total cost of all medicine items claimed respectively for 2005 and 2006 (refer to table 4.3.3). Even though the total cost of isotretinoin only represented a relatively small portion of the total cost of the database, isotretinoin still showed a cost-prevalence index (CPI) value of more than 1 in both years (CPI = 3.30 for 2005 and CPI = 2.92 for 2006) indicating and supporting that isotretinoin is an expensive medicine although found to be cost effective in severe acne (Wessels et al., 1999:794, refer to section 2.7.8 and for an explanation of CPI refer to section 3.5.2.3)

The total cost of isotretinoin items claimed decreased by 4.1% over the two study years, although the total number of isotretinoin prescriptions claimed increased by 8.8% (refer to section 4.2.3). This decrease in total cost of isotretinoin items claimed was in contrast to the 8.1% increase of the total cost of all medicine items claimed on the total database, indicating that there is an overall decrease in the cost burden isotretinoin has on medical funders.

In total, isotretinoin cost had a burden to funders, estimated at R56 000 and R52 000 per 10 000 beneficiaries respectively for the year 2005 and 2006. The cost per beneficiary (per patient) claiming through the database (PMB), for all medicines claimed, was estimated at R1 554 and R1 626 respectively for 2005 and 2006. This cost per utilising beneficiary indicated the average cost per patient that was part of one of the medical schemes included in the PBM database.

4.4 PRESCRIBING PATTERNS OF THE DIFFERENT TYPES OF ISOTRETINOIN MEDICINE ITEMS

4.4.1 Different types of isotretinoin medicine items

The generic systemic isotretinoin items were prescribed at a higher rate in relation to the innovator systemic isotretinoin medicine items (refer to table 4.4). Two generic products for systemic isotretinoin items were available (these generics became available at the end of 2002), namely Acnetane® and Oratane®. Note that early in 2008 another generic form of systemic isotretinoin entered the market, namely Tretoderm®. This product fell outside the study period and is therefore not included. This could, however, indicates that the increased use of isotretinoin (also seen in section 4.2.3 and 4.2.4) justified the introduction of another generic to the market.

Table 4.4: Prescribing patterns and cost of the different types of isotretinoin products for 2005 and 2006.

Year	Isotretinoin medicine type	Number of isotretinoin items	%*	Average cost per item (R)	Total cost (R)	%**
2005	**Innovator** (Roaccutane®)	7 517	34.8	394.99 ± 240.75	2 969 166	43.6
2006	**Innovator** (Roaccutane®)	7 163	30.4	359.76 ± 237.89	2 576 926	39.4
2005	**Generic** (Acnetane®, Oratane®)	13 406	62.0	281.16 ± 169.49	3 769 238	55.4
2006	**Generic** (Acnetane®, Oratane®)	15 483	65.8	250.15 ± 156.12	3 873 147	59.3
2005	**Non-generic** (Isotrex® gel)	709	3.3	101.11 ± 29.31	71 686	1.1
2006	**Non-generic** (Isotrex® gel)	886	3.8	93.87 ± 25.32	83 169	1.3

*Percentage was calculated according to the total number of isotretinoin items claimed for the specific year.

**Percentage was calculated according to the total cost of isotretinoin items claimed for the specific year.

A decrease of 12.6% in the percentage of the total number of innovator isotretinoin items claimed was seen from 2005 to 2006, indicating that the innovator isotretinoin items were claimed at a lower percentage in 2006 than in 2005 (refer to table 4.4).

With this decrease in the innovator isotretinoin items claimed, an increase of 6.1% occurred in the percentage of generic isotretinoin items claimed (refer to table 4.4). Even though this was merely a two year study period a trend could already be identified, indicating a shift towards generic usage in systemic isotretinoin medicine items.

The difference between innovator and generic systemic isotretinoin items claimed indicated a 1.8:1 (for 2005) and 2.2:1(for 2006) ratio of generic systemic isotretinoin products claimed versus innovator systemic isotretinoin products claimed. Although this ratio could indicate that generic systemic isotretinoin was claimed at a relative high ratio, it still indicated a lower ratio in relation to the generic vs. innovator claims of all medicine items at 3:1 on the database. The innovator systemic isotretinoin items were therefore claimed at a higher percentage of isotretinoin claims in relation to the percentage of innovator medicine items claimed on the total database.

Systemic isotretinoin had an average cost per original isotretinoin item of R394.99 ± 240.75 and R359.76 ± 237.89 respectively for 2005 and 2006 (refer to table 4.4). This average cost per innovator isotretinoin item showed a decrease of 8.91% (R35.23) from 2005 to 2006 (refer to table 4.4).

There was an even larger decrease of 11.03% (R31.01) in the average cost per generic medicine item from 2005 (R281.16 ± 169.49) to 2006 (R250.15 ± 156.12) (refer to table 4.4). Reasons for this occurrence are not fully known; however, the influence of the single exit price (although incorporated in both study years) and market influences may have played a role (the single exit price decreased more for generic products than for originator products), as well as treatment aspects.

The difference in average cost between the original and the generic form of systemic isotretinoin showed that the generic form was about 30% more "affordable" than the original systemic isotretinoin product for the study years, at 28.8% in 2005 and at 30.5% in 2006. This percentage difference was lower than the difference in average cost between all innovator and generic medicine items on the database which indicated a difference of 50% between the average cost of the entire innovator and generic medicine items claimed.

This cost difference between innovator and generic systemic isotretinoin, indicates that if the innovator systemic isotretinoin medicine items had been replaced by the generic systemic isotretinoin medicine items a certain amount of cost could have been saved. If a scenario is created for the year 2006, the potential savings can be calculated for illustration purposes.

Scenario: If accepted that the treatment regimen of the different systemic isotretinoin types (mg/day and treatment period) were the same, a scenario could be created. If 50% of the innovator systemic isotretinoin medicine items had been substituted for the generic isotretinoin medicine items in the year 2006, an estimated 3 582 innovator isotretinoin items would be replaced. By taking the 30.5% difference in average cost for the year 2006 into consideration, it is calculated that an estimated R400 000 could have been saved in the year 2006 by only replacing 50% of innovator isotretinoin products. This scenario indicates the importance of a shift towards generic isotretinoin usage.

The original isotretinoin medicine items represented 43.6% and 39.4% of the total cost of isotretinoin medicine items respectively for 2005 and 2006. In relation to this, the generic isotretinoin medicine items represented 55.3% and 59.3% of the total cost of isotretinoin medicine items respectively in 2005 and 2006 (refer to table 4.4 for total cost). The relatively small decrease seen in original isotretinoin medicine items' total cost and the relatively small increase seen in generic isotretinoin medicine items' total cost, correlated with the slight decrease and increase in the number of isotretinoin items claimed.

The non-generic (Isotrex® gel), the only topical form of isotretinoin, will be discussed in the next section (section 4.6.1).

4.5 PRESCRIBING PATTERNS OF THE DIFFERENT ISOTRETINOIN PRODUCTS

4.5.1 Prescribing patterns of Isotrex® gel

The topical form of isotretinoin, Isotrex® gel, represented 3.3% and 3.8% of all isotretinoin products respectively in 2005 and 2006 (refer to table 4.5). This relatively low prevalence was much lower in relation to any other isotretinoin products claimed over both study years. This can be a result of the following – topical isotretinoin has a low effectiveness in relation to the systemic form of isotretinoin (Gollnick *et al.*, 2003:S5) and therefore it would be prescribed at a lower rate in relation to the systemic isotretinoin. Topical isotretinoin is only as effective as the topical retinoid, adapalene, which has less of a skin irritation effect than topical isotretinoin and may therefore be preferred as treatment (Io Annides *et al.*, 2002:526, refer to section 2.6).

The total number of Isotrex® gel items claimed increased by 25% from 2005 (n = 709) to 2006 (n = 886), but only represent a slightly higher percentage (from 3.3% to 3.8%) of the total number of isotretinoin items claimed respectively for 2005 and 2006 (refer to table 4.5).

Table 4.5: The total number, average cost and total cost of the different isotretinoin products claimed in the years 2005 and 2006.

Year	Drug type (®)	Total number of *isotretinoin* items (n)	%*	Average cost per *isotretinoin* item (R)	Total cost of *isotretinoin* items (R)	%**
2005	Isotrex gel	709	3.3	101.11 ± 29.31	71 686	1.1
	Roaccutane 10mg	1 830	8.5	169.93 ± 72.12	310 979	4.6
	Roaccutane 20mg	5 687	26.3	467.14 ± 231.08	2 658 187	39.0
		(7 517)	**(34.8)**		**(2 969 166)**	**(43.6)**
	Acnetane 10mg	1 821	8.4	114.19 ± 48.71	207 939	3.1
	Acnetane 20mg	5 187	24.0	341.69 ± 157.03	1 772 334	26.0
		(7 008)	**(32.4)**		**(1 980 273)**	**(29.1)**
	Oratane 10mg	1 775	8.2	115.01 ± 51.86	204 141	3.0
	Oratane 20mg	4 623	21.4	342.81 ± 155.52	1 584 825	23.3
		(6 398)	**(29.6)**		**(1 788 966)**	**(26.3)**
	Total	**21 632**	**100**		**6 810 090**	**100**
2006	Isotrex gel	886	3.8	93.87 ± 25.32	83 169	1.3
	Roaccutane 10mg	1 803	7.7	158.60 ± 74.23	285 947	4.4
	Roaccutane 20mg	5 360	22.8	427.42 ± 235.77	2 290 978	35.1
		(7 163)	**(30.4)**		**(2 576 925)**	**(39.5)**
	Acnetane 10mg	2 282	9.7	102.45 ± 47.71	233 792	3.6
	Acnetane 20mg	6 161	26.2	299.62 ± 146.30	1 845 952	28.3
		(8 443)	**(35.9)**		**(2 079 744)**	**(31.8)**
	Oratane 10mg	1 885	8.0	104.48 ± 47.70	196 945	3.0
	Oratane 20mg	5 155	21.9	309.69 ± 148.00	1 596 458	24.4
		(7 040)	**(29.9)**		**(1 793 403)**	**(27.4)**
	Total	**23 532**	**100**		**6 533 241**	**100**

*Percentage was calculated according to the total number of isotretinoin product claims for the specific year.

**Percentage was calculated according to the total cost of isotretinoin product claims for the specific year.

The average cost per Isotrex® gel item decreased from R101.11±29.31 to R93.87±25.32 from 2005 to 2006 (d-value of 0.2). This correlates with the decreases identified in average cost of the systemic isotretinoin products from 2005 to 2006 (refer to table 4.5).

The total cost of Isotrex® gel items only represented 1.1% (R 71 686) and 1.3% (R 83 169) of the total cost of isotretinoin products respectively for 2005 and 2006 (refer to table 4.5). The cost-prevalence index for Isotrex® gel was less than one (<1), at 0.32 in 2005 and 0.34 in 2006 in relation to all other isotretinoin products, indicating that the topical form of

isotretinoin was relatively inexpensive if compared to the systemic isotretinoin forms. Even so the topical form of isotretinoin was still claimed at a relatively low rate and only had a small effect on isotretinoin prescribing patterns overall. The treatment value of this product in combination with other acne products should be further investigated as related to outcomes and cost.

4.5.2 Prescribing patterns of Roaccutane®, Acnetane® and Oratane®

The innovator drug (Roaccutane®) had the highest percentage of isotretinoin items claimed for 2005 at 34.8% in relation to Acnetane® at 32.4% and Oratane® at 29.6%. For the year 2006, Acnetane® had the highest percentage of isotretinoin items, at 35.9%, followed by Roaccutane® at 30.4% and then Oratane® with still the lowest amount claimed at 29.9% (refer to table 4.5).

The 20mg strength of the systemic isotretinoin products was claimed in approximately 74% of the cases in relation to all the systemic isotretinoin products in both study years. According to a study done in the USA, the indications were that a 40mg capsule (not available in South Africa) where prescribed in 78% of mentions, followed by 14% for the 20mg and 4% for the 10mg (Wysowski *et al.,* 2002:508, refer to section 2.7.5).

The average cost per 20mg isotretinoin item claimed for Roaccutane® was R467.14 ± 231.08 and R427.42 ± 235.77 respectively in 2005 and 2006 in relation to the 10mg isotretinoin items of Roaccutane® at R169.93 ± 72.12 and R158.60 ± 74.23 respectively for 2005 and 2006 (refer to table 4.5).

This relatively large difference in average cost, between the different strengths, was due to the higher average number of capsules per prescription for the 20mg strength of systemic isotretinoin. It indicated that for Roaccutane® the 10mg capsules were claimed at an average just over 30 capsules per prescription over both study years(refer to table 4.7). In relation the Roaccutane® 20mg capsules had a higher average number of capsules per prescription of about 53 and 51 capsules per prescription respectively for 2005 and 2006 (refer to table 4.7). This was the reason for the relatively large difference in average cost between the 10mg and 20mg isotretinoin items for Roaccutane®. The same tendency was seen in Acnetane® and Oratane® (refer to table 4.7).

The high percentage of 20mg capsules claimed and the high number of 20mg capsules per prescription show the need to introduce a 40mg capsule onto the South Africa market as is

available in the USA, especially if a 40mg capsule will be cost saving in relation to the usage of two 20mg capsules.

The average cost differences of the different strengths of the isotretinion products are shown in table 4.5, between Roaccutane®, Acnetane® and Oratane®. Over both the study years the results indicated that the average cost of Acnetane® was the lowest in relation to the other systemic isotretinoin products, therefore these results indicate that Acnetane® may be the product (generic) with the most cost-saving possibilities on the market for systemic isotretinoin, even though the difference was relatively small when compared to the other generic, Oratane®.

Acnetane® indicated the largest increase in the number of isotretinoin items, with a increase of 20.5% (from n = 7 008 to n = 8 443 respectively for 2005 and 2006) in relation to a decrease in the in Roaccutane® (the innovator) of 4.7% and only a 10.0% (n = 6 398 to n = 7 040 respectively for 2005 and 2006) increase by the other generic, Oratane®. Acnetane® was also claimed at a higher rate in relation to the other generic product, Oratane® (refer to table 4.5).

Of the three oral products available for systemic isotretinoin, Roaccutane® played the leading role in the total cost of the isotretinoin products over both study years at 43.6% and 39.5% respectively in 2005 and 2006. There was a decrease in the total cost of Roaccutane® products, as noted before (refer to innovator products in section 4.4.2), in relation to the increases indicated in both Acnetane® and Oratane® products over the two year study period (refer to table 4.5).

4.5.3 Prescribing patterns of the combination of 10mg and 20mg systemic isotretinoin capsules.

The combination of 10mg and 20mg isotretinoin capsules was prescribed and claimed together in 2 700 and 2 978 prescriptions respectively for 2005 and 2006. The total number for each individual isotretinoin product, combined in different strengths, can be seen in Table 4.6. This combination occurred in 14.5% and 14.7% of all isotretinoin prescriptions claimed through the database respectively for 2005 and 2006 (for total numbers of isotretinoin prescriptions refer to table 4.1). As stated before the combination of 10mg and 20mg isotretinoin capsules was used to reach the desired daily dose, two scenarios were created in the example table (dosage regimes followed is indicated in Gibbon *ed.*, 2005:194, refer to section 2.4.4).

Example table: Different combinations of systemic isotretinoin treatment regimen.

Weight of patient	Daily dosage used	Isotretinoin dosage forms used to reach desired daily dosage
50kg	1 mg/kg/day (50 mg daily)	2x20mg capsules, 1x10mg capsules
60kg	0.5 mg/kg/day (30 mg daily)	1x20mg capsules, 1x10mg capsules

The average cost per prescription of this combination was relatively high (CPI >1) in relation to the average cost per isotretinoin prescription. The lowest average cost per prescription containing a combination was Acnetane® and the highest was Roaccutane® respectively for 2005 and 2006 (refer to table 4.6). This higher average cost of combinations in relation to the average cost of all isotretinoin products (refer to section 4.4.1), are due to a possible higer daily dosage and/or the lower cost of topical isotretinoin was not taken into consideration.

Table 4.6: Prescribing patterns of isotretinoin 10mg and 20mg capsule combinations in 2005 and 2006.

Year	Isotretinoin product combination (10mg and 20mg)	Total number of combination prescriptions	Average cost per combination prescription (R)
2005	Acnetane®	870	415.45 ± 158.97
	Oratane®	824	416.95 ± 141.15
	Roaccutane®	1 006	603.98 ± 222.91
	Total	**2 700 (14.5%)***	
2006	Acnetane®	1 015	352.63 ± 154.70
	Oratane®	955	384.15 ± 154.83
	Roaccutane®	1 008	546.06 ± 240.82
	Total	**2 978 (14.7%)***	

*Percentage was calculate according to the total number of isotretinoin prescriptions claimed for the specific year.

These combinations indicate why there is a difference between the total number of isotretinoin items and total number of isotretinoin prescriptions (refer to table 4.1). These combinations results refer only to prescriptions which contained both strengths of oral isotretinoin. Combinations with other medicine items were evaluated in section 4.10.

4.5.4 Average cost per single capsule of isotretinoin

The fact that patients have different prescribed daily dosages because of their different weights and the different recommended dosage regimes that could be followed (between 0.5 to 1 mg/kg/day), it was therefore necessary to identify the average cost per capsule. This would indicate the average cost difference between the three systemic isotretinoin products, without the role of patient weight and daily dosage affecting the average cost.

Table 4.7: Average cost per single capsule of systemic isotretinoin products for 2005 and 2006.

Year	Product description (®)	Number of isotretinoin items	Average number of capsules per prescription	Cost per capsule (R)
2005	Acnetane 10mg	1 821	31.26 ± 14.22	3.70 ± 0.47
	Acnetane 20mg	5 187	54.87 ± 26.32	6.40 ± 0.82
	Total	**7 008**		
	Oratane 10mg	1 775	31.64 ± 15.09	3.68 ± 0.44
	Oratane 20mg	4 623	55.62 ± 26.32	6.35 ± 0.84
	Total	**6 398**		
	Roaccutane 10mg	1 830	30.71 ± 14.64	5.64 ± 0.55
	Roaccutane 20mg	5 687	53.04 ± 27.44	9.09 ± 0.93
	Total	**7 517**		
2006	Acnetane 10mg	2 282	31.38 ± 14.16	3.29 ± 0.70
	Acnetane 20mg	6 161	52.80 ± 25.66	5.84 ± 1.14
	Total	**8 443**		
	Oratane 10mg	1 885	31.49 ± 14.87	3.36 ± 0.56
	Oratane 20mg	5 155	54.65 ± 25.95	5.83 ± 1.12
	Total	**7 040**		
	Roaccutane 10mg	1 803	30.71 ± 13.40	5.23 ± 1.28
	Roaccutane 20mg	5 360	51.06 ± 27.12	8.66 ± 1.93
	Total	**7 163**		

As expected Roaccutane® had the highest average cost per capsule (refer to table 4.7), with a practical significant cost difference (d-value of >1) in relation to both the strengths (10mg and 20mg) of Acnetane® and Oratane®. The d-values were 3.53 and 3.56 between the

10mg capsule of Roaccutane® and the 10mg capsule of Acnetane® and Oratane® respectively in 2005 and d-values of 1.52 and 1.46 respectively in 2006. The d-values between the 20mg Roaccutane® and 20mg Acnetane® and Oratane® respectively were 2.89 and 2.95 for 2005 and 1.46 and 1.47 for 2006. This indicates a significant cost difference between the average cost per isotretinoin capsule of the generic and innovator products.

The relatively small difference in average cost per isotretinoin capsule between the generic products, Acnetane® and Oratane®, was practically insignificant (d-value in both years were less than 0.2). This indicates that the generics had no significant cost differences.

The average number of capsules per prescriptions did indicate that the two generic systemic isotretinoin items had a slightly higher average number of capsules prescribed in both the 10mg and 20mg strengths (refer to table 4.7). The lower cost of the generic isotretinoin items may be the reason that the two oral generic forms of isotretinoin were prescribed at a slightly higher average number of capsules per prescriptions (this also indicates a higher average daily dose). It is recommended to do further studies on the effect cost (including the single exit price) may have on the decision to prescribe higher daily dosages of systemic isotretinoin.

4.6 ANALYSIS OF THE PRESCRIBING PATTERNS OF ISOTRETINOIN PRODUCTS ACCORDING TO DIFFERENT PRESCRIBERS

For the purpose of data analysis all prescribers were divided into the following groups, (1) general medical practitioners, (2) dermatologists and the (3) other group including all the other medical specialised prescribers registered. The main focus was on the dermatologists and general medical practitioners, where the analysis focused on potential defferences in their prescribing patterns.

4.6.1 *Number of isotretinoin prescriptions*

Dermatologists prescribed the highest percentage of isotretinoin prescriptions over both study years; prescribing 68.2% and 65.7% of isotretinoin prescriptions respectively in 2005 and 2006 (refer to table 4.8). These patterns indicate a slight decrease in the percentage of isotretinoin prescriptions prescribed by dermatologists over the two study years.

However, this indicates that a relatively high percentage of prescriptions were prescribed by dermatologists and it could indicate that patients with severe acne (indication for isotretinoin use) were more likely to be referred by general practitioners or approached dermatologists directly. It could also indicate that dermatologists were more likely to prescribe isotretinoin to their acne patients.

In the USA nearly 90% of isotretinoin prescriptions were prescribed by dermatologists (Wysowski *et al.*, 2002:507) and in relation to this the percentage of prescriptions prescribed by dermatologists was much lower in this section of the private heathcare sector of South Africa. This phenomenon was not investigated, but one of the reasons for a relatively lower percentage of prescriptions by dermatologists may be because there are only about 165 dermatologists registered in South Africa (Dermatology society of South Africa, 2008) in relation to more than 5 000 registered general practitioners (HPCSA, 2008). Other reasons may be the nature of the patients' condition or the possible severe side-effects of isotretinoin influencing the choice of prescriber.

Table 4.8: The prevalence and average cost of isotretinoin containing prescriptions according to the prescriber for 2005 and 2006

Year	Prescriber	Total number of isotretinoin prescriptions	Percentage (%)**	Average cost per isotretinoin prescription (R)	Total cost (R)
2005	**Dermatologist**	12 678	68.2	388.04 ± 227.57	4 919 588
	General Medical Practitioner	5 102	27.5	317.42 ± 200.52	1 619 478
	Other*	809	4.4	328.15 ± 234.94	263 508
2006	**Dermatologist**	13 283	65.7	341.84 ± 216.76	4 540 599
	General Medical Practitioner	6 009	29.7	283.10 ± 184.00	1 701 127
	Other*	940	4.6	304.24 ± 208.25	281 114

*Other includes all other registered prescribers excluding dermatologists and GP's.

**Percentage was calculated according to the total number of isotretinoin prescriptions for the specific year.

-Note that pharmacists did not play a role because pharmacists has no authority to prescribe isotretinoin (isotretinoin is a schedule 5 drug)

The general practitioners (GP) prescribed 27.5% and 29.7% of isotretinoin prescriptions respectively for 2005 and 2006 (refer to table 4.8). This was much higher in relation to the

study done by Wysowski *et al.* (2002:507), in the USA, which indicated that only about 8% of isotretinoin prescriptions were prescribed by general practitioners.

4.6.2 Average cost per isotretinoin prescription

General practitioners had a lower average cost per prescription containing isotretinoin in relation to dermatologists; at R317.42 ± 200.52 and R283.10 ± 184.00 for GPs compared to R388.04 ± 227.57 and R341.84 ± 216.76 for dermatologists respectively for 2005 and 2006 (refer to table 4.8). The average cost per prescription for dermatologists and general practitioners showed a difference of R70.62 (18.2%) for 2005 and R58.74 (17.2%) for 2006. Reasons for this higher average cost per isotretinoin prescription could be due to dermatologists prescribing fewer generic isotretinoin items (refer in section 4.6.4) and/or there could be a difference in average daily dosage prescribed. This could not be evaluated. The d-value of 0.31 (2005) and 0.27 (2006) between this average cost per isotretinion prescription for dermatologists and general practitioners indicated that the cost difference may be practically significant in both of the study years.

Because dermatologists had the highest number of prescriptions prescribed and the highest average cost per isotretinoin prescription the dermatologists also had the biggest influence on the total cost of isotretinoin products at 72.2% (R4 919 588) and 69.5% (R4 540 599) respectively for 2005 and 2006 (refer to table 4.8).

The influence of the other prescribers on the number of isotretinoin prescriptions was relatively low at only 4.4% and 4.6% respectively for 2005 and 2006 (refer to table 4.8). The other prescribers included other types of specialists such as e.g. oncologists, neurologists, endocrinologists and orthopaedists.

4.6.3 Difference in prescribing of acne medicine

The tendency in the case of prescriptions containing any of the identified acne preparations was reversed. Dermatologists only prescribed 30.8% and 30.6% of all identified anti-acne prescriptions respectively for the study years of 2005 and 2006 (refer to table 4.9). Note that acne medication was classified according to the MIMS® classification (refer to section 3.5.1.1) and certain products that could also be used as acne treatment was not taken into account.

This was still a retatively high percentage of acne medications prescribed by dermatologists, even though there are only 165 registered dermatologists in South Africa (Dermatology society of South Africa, 2008), but the literature studies done in America indicated that most visits to dermatologists were acne related (Pal, 1997:4)refer to introduction, section 1.2).

In comparison the general practitioners prescribed 56.6% and 55.8% of acne medicine containing prescriptions respectively for 2005 and 2006. For the total number of acne medications, general practitioners played the biggest role in prescribing anti-acne medications while dermatologists played the biggest role in the prescribing of isotretinoin (refer to table 4.10).

Table 4.9: Average cost and number of medicine items per acne prescription claimed according to different prescribers for the years 2005 and 2006.

Year	Prescriber	Number of acne prescriptions (n)	%**	Average cost per acne prescription(R)	Average number of acne medicine items per prescription
2005	**Dermatologists**	34 332	30.8	253.06 ± 192.76	1.25 ± 0.51
	General Medical Practitioner	63 178	56.6	145.55 ± 104.84	1.10 ± 0.33
	Other	10 090	9.0	147.82 ± 111.12	1.08 ± 0.29
	Pharmacy*	4 018	3.6	96.91 ± 52.71	1.05 ± 0.23
	Total	**111 618**	**100**		
2006	**Dermatologists**	33 044	30.6	237.90 ± 181.19	1.26 ± 0.51
	General Medical Practitioner	60 152	55.8	137.45 ± 102.46	1.10 ± 0.34
	Other	10 176	9.4	137.57 ± 108.16	1.07 ± 0.29
	Pharmacy*	4 460	4.1	95.40 ± 54.93	1.08 ± 0.29
	Total	**107 832**	**100**		

*Pharmacy refers to pharmacist

**Percentage was calculated according to the total number of acne prescriptions claimed for the specific year.

The higher average cost per acne prescription prescribed by dermatologists in relation to general practitioners (refer to table 4.9) could be due to the high number of isotretinoin prescriptions prescribed by dermatologists (refer to section 4.6.1) and/or the relatively higher average number of acne items per prescription (refer to table 4.9). The average cost of acne prescriptions for both the general practitioners or other prescribers and the dermatologists

idicated a d-value of about 0.5, indicating that the average cost difference was observable and may be of practical significance in both of the study years.

Pharmacies (which suggests Pharmacists) prescribed and claimed acne medications at the lowest percentage of 3.6% (n = 4 018) and 4.1% (n = 4 460) in relation to the registered prescribers respectively for 2005 and 2006 (Pharmacists are not allowed to prescribe antibiotics or isotretinoin for acne). The average cost per acne prescription claimed of the different prescribers, including pharmacists (pharmacy) are indicated in table 4.9.

Dermatologists prescribed a higher average number of acne medicine items per prescription at 1.25 ± 0.51 and 1.26 ± 0.51 respectively for 2005 and 2006. This higher average number of acne medicine items per prescription by dermatologists indicates that dermatologists were more likely to prescribe combination acne medication compared to the general practitioners. The different acne medicine combinations and the different acne products prescribed by the different prescribers fell outside the scope of this study.

4.6.4 Difference in prescribing patterns of the innovator and generic isotretinoin medicine items

As indicated before, dermatologists prescribed about two-thirds of isotretinoin prescriptions over the two study years and therefore also played the major role in isotretinoin costs (as seen in section 4.7.1.).

Dermatologists prescribed the innovator isotretinoin items at a higher percentage of 38.1% (n = 5 675) and 33.8% (n = 5 260) in relation to the general medical practitioners of 25.1% (n = 1 454) and 22.2% (n = 1 528) respectively for 2005 and 2006 (refer table 4.10). This indicates that dermatologists may have a preference for prescribing the innovator isotretinoin medicine items than the general practitioners. Reasons for this are unknown, but one of the reasons may be that a general perception may exist; believing that the innovator isotretinoin product is of higher quality and provide better outcomes. This phenomenon fell outside the scope of the study. A recent study indicated that there are differences between some generic isotretinoin products and the innovator product (the study did not include one of the generics available in South Africa) (Taylor & Keenan, 2006:603, refer to section 2.7.6).

The dermatologists did show a relatively small increase in prescribing the generic type of isotretinoin medicine items over the two study years with an increase of 3.7% in the percentage difference of generic isotretinoin items. This increase may indicate that dermatologists may become less reluctant to prescribe the generic forms of isotretinoin. In

contrast general medical practitioners prescribed the generic forms of isotretinoin at a higher percentage of 68.9% and 72.1% respectively for 2005 and 2006 (refer to table 4.10).

Table 4.10: The number and percentage of generic isotretinoin products prescribed by dermatologists and general medical practitioners for 2005 and 2006

Year	Generic indicator	Dermatologists		General medical practitioners	
		Number of items (n)	(%)*	Number of items (n)	Percentage (%)*
2005	Original	5 675	38.1	1 454	25.1
	Generic	8 900	59.7	3 989	68.9
	Non-generic (topical)	335	2.2	346	6.0
	Total	14 910	100	5 789	100
2006	Original	5 260	33.8	1 528	22.2
	Generic	9 869	63.4	4 951	72.1
	Non-generic (topical)	448	2.9	390	5.7
	Total	15 577	100	6 869	100

*Percentage calculated according to the total number of isotretinoin items prescribed by dermatologist or by general practitioners in the specific year.

The original:generic isotretinoin items ratio for the general practitioners over both the study years indicated that for every original systemic isotretinoin product prescribed there were 2.7 and 3.2 generic products prescribed and claimed respectively for 2005 and 2006. This correlates closely with the original:generic ratio of the total database indicating that for every original medicine item prescribed and claimed, 3.0 generic medicine items were prescribed and claimed (mentioned also in section 4.4.1).

The topical form of isotretinoin, which had no generic available, was prescribed at a higher percentage by general practitioners at 6.0% and 5.7% in relation to the dermatologists where it was only prescribed at 2.2% and 2.9% respectively for 2005 and 2006 (refer to table 4.10). There was only a slight difference in the percentage of the non-generic topical isotretinoin medicine items prescribed respectively by the dermatologists and general practitioners. These relatively low rate of prescribing the topical form of isotretinoin could be due to the literature's indications that the topical form of isotretinoin is not as effective as the systemic isotretinoin and that adapalene (Differen®) should rather be used in place of the topical form of isotretinoin because of fewer skin irritations (Io Annides et al., 2002:526, refer tosection 2.6 and also mentioned in section 4.5.1).

4.7 THE PRESCRIBING PATTERNS OF ISOTRETINOIN AND ACNE MEDICINE FOR DIFFERENT AGE GROUPS

The data were divided into different age groups, to identify certain prescribing patterns of isotretinoin. The different age groups included the following:

Age group one	(1):	>0 to ≤2 years
Age group two	(2):	>12 to ≤9 years
Age group three	(3):	>19 to ≤27 years
Age group four	(4):	>27 to ≤35 years
Age group five	(5):	>35 years

(Note that if a patient happens to be for example 12 years and one day on the date he/she claimed their prescription, that patient would be classified in age group 2 (older than 12 years), this separation also applies to the other age groups)

4.7.1 Prescribing patterns as reflected in isotretinoin prescriptions per age group

Over the two study years there were 131 isotretinoin prescriptions claimed for patients under the age of twelve years even though the use of isotretinoin in pediatric patients younger than 12 years of age has not been studied. New guidelines from a European directive (Leyton *et al.*, 2006:774) stated that isotretinoin is not recommended in children younger than 12 years of age (refer to section 2.7.7, table 2.7). Even though the number of prescriptions decreased for the age group younger than 12 years, from 79 to 52 respectively in 2005 and 2006, this small number could still be a concern (refer to table 4.11).

The teenage-group of 12 to 19 years (age group 2) had the largest number of isotretinoin prescriptions claimed in relation to the other age groups in both the study years (refer to table 4.11). This age group claimed almost half of all the isotretinoin prescriptions on the database, at 48.4% (n = 8 989) and 47.7% (n = 9 656) of claims respectively for the years 2005 and 2006 (refer to table 4.11). For this age group the high number of isotretinoin prescriptions claimed was in close proximity to figures in the USA, where 60% of patients treated with isotretinoin were in the age group 10 to 19 years (Fleischer *et al.,* 2003:665. refer to section 2.7.2).

Table 4.11: Prescribing patterns of prescriptions containing isotretinoin according to patient age groups for 2005 and 2006

Year	Age group	Number of isotretinoin prescriptions (n)	Percentage number (%)*	Average cost per prescription (R)	Total cost (R)
2005	**1**	79	0.42	352.25 ± 213.98	27 828
	2	8 989	48.4	389.03 ± 214.85	3 497 074
	3	4 969	26.7	374.80 ± 220.22	1 862 378
	4	1 597	8.6	373.12 ± 248.24	595 874
	5	2 955	15.9	279.84 ± 220.57	826 936
	Total	**18 589**	**100**		**6 810 090**
2006	**1**	52	0.26	221.50 ± 180.72	11 518
	2	9 656	47.7	343.99 ± 207.09	3 321 565
	3	5 645	27.9	330.26 ± 207.68	1 864 318
	4	1 755	8.7	319.56 ± 216.04	560 830
	5	3 124	15.4	248.01 ± 196.15	775 010
	Total	**20 232**	**100**		**6 533 241**

*Percentage calculated according to the total number of isotretinoin prescriptions for the specific year.

The combination of age group 2 together with age group 3, which includes the ages of 12 to 27 years, represented 75.1% and 75.6% of isotretinoin prescriptions claimed respectively for 2005 and 2006. The high prevalence rate of isotretinoin prescriptions claimed in this combined age group could be expected and correlates with the literature where acne is most prevalent in the age group 12 to 24 years (Pal, 1997:4, refer to section 2.3.1).

Age group 3 showed the largest increase of 13.6% in the number of isotretinoin prescriptions claimed over the two study years. This higher increase in age group 3 may indicate a shift towards isotretinoin prescribing towards slightly older patients over the two-year study period, also supported by the decrease in percentage in age group 2 (refer to table 4.11). Reason(s) for this occurrence was unknown and a longer study period would possibly be required to investigate this aspect.

The total database indicated that 71.6% (n = 6 103 813) and 72.1% (n = 6 522 821) of prescriptions were claimed for the age group above 35 years of age (age group 5) (refer to appendix A, table A2). In comparison, age group 2 represented only 5.1% (n = 435 904 in 2005 and n = 459 205 in 2006) of all prescriptions claimed in both study years (refer to appendix A, table A2). Of this total number of prescriptions in age group 2, 2.1% were isotretinoin prescriptions in 2005 and 2006. In this specific age group isotretinoin

prescriptions represented a higher percentage (2.1%) of prescriptions in comparison to any of the other age groups. The total database (including all age groups) indicated that isotretinoin prescriptions represented 0.22% of all prescriptions in 2005 and 2006 (refer to section 4.3, table 4.1).

This indicates the major role isotretinoin treatment plays in the teenage years in comparison to all other age groups.

4.7.2 Cost of isotretinoin products per age group

Age group 2 (12 to 19 years) had the highest average cost per isotretinoin prescription of R389.03 ± 214.85 and R343.99 ± 207.09 respectively for 2005 and 2006 in relation to all the other age groups (refer to table 4.11). From this age group onward the average cost per isotretinoin prescription decreased with the increase in the age groups (refer to table 4.11). There was no practical significant difference between the average costs of the different age groups for both 2005 and 2006 (d-value of less than 0.2 between age groups), except for the average cost difference between age group 2 (12 to 19 years), 3 (19 to 27 years) and 4 (27 to 35 years) in comparison with age group 5 (above 35 years) which was observable and may be a practical significant difference.

The largest number of isotretinoin prescriptions and the highest average cost per isotretinoin prescription claimed were encountered in age group 2; therefore this age group also represented the highest total cost for isotretinoin prescriptions per age group at 51.4% (R3 497 074) and 50.8% (R3 321 565) of the total cost of isotretinoin respectively for 2005 and 2006 (refer to table 4.11). This indicated that a CPI value of 1.06 was reached in comparison to the value of 0.75 for the total database for this age group over both study years. The CPI value indicated that isotretinoin cost in age group 2 was expensive in comparison to an inexpensive medicine cost calculated in this age group on the total database. The CPI of isotretinoin cost was lower in all age groups in relation to the CPI of the total database for that specific age group, except for age group 5 (ages above 35 years) where the CPI of isotretinoin cost was lower at 0.76 in relation to the CPI of 1.11 of the total database. Reasons for this effect could be due to a higher comsumption rate of chronic medicine used in this age group above 35 years (refer to the higher average number of prescriptions per patient for the age group above 35 years in table A2 in Appendix A).

The total cost of isotretinoin in the age group of 12 to 19 years, represented 4.8% and 4.3% of the total cost of all medicine claimed in this age group respectively for 2005 and 2006

(calculated from table 4.11 and table A2 in Appendix A), indicating the relatively high effect isotretinoin costs have in this specific age group.

This indicates that isotretinoin had a relative high estimated cost of R275 000 and R260 000 per 10 000 beneficiaries in the teenage group 12 to 19 years respectively for 2005 and 2006. To put this in perspective and compare this cost to the age group >35 years, where acne occurs in fewer than 3% of persons (Pal, 1997:4, refer to section 2.3.1), isotretinoin cost only indicated a cost of R12 500 and R11 100 per 10 000 beneficiaries in the age group above 35 years respectively for 2005 and 2006.

4.7.3 Prescribing patterns of acne prescriptions in relation to isotretinoin prescriptions per age group

For acne prescriptions age group 2 also had the highest number of acne prescriptions (refer to table 4.12). As expected the age group younger than 12 years had the smallest number of acne prescriptions at 1.0% and 0.9% respectively for 2005 and 2006, this is because acne usually starts at the onset of puberty (Wolff *et al.*, 2005:2, refer to section 2.3.1).

Table 4.12: Number of acne prescriptions in relation to prescriptions containing isotretinoin for 2005 and 2006.

Year	Age group	Number of acne prescriptions	%*	Number of isotretinoin prescriptions	%**
2005	1	1 126	1.0	79	7.0
	2	37 827	33.9	8 989	23.8
	3	33 207	29.8	4 969	15.0
	4	13 923	12.5	1 597	11.5
	5	25 535	22.9	2 955	11.6
	Total	**111 618**	**100**	**18 589**	**16.7**
2006	1	1 000	0.9	52	5.2
	2	36 354	33.7	9 656	26.6
	3	33 056	30.7	5 645	17.1
	4	13 006	12.1	1 755	13.5
	5	24 417	22.6	3 125	12.8
	Total	**107 833**	**100**	**20 233**	**18.8**

*Percentage was calculated according to the total number of acne prescriptions claimed during the specific year.

**Percentage was calculated according to the number of isotretinoin containing prescriptions in relation to acne prescriptions for the specific age group in the specific year.

Age group 5, which was the largest age group including all the ages above 35 years, only represented 22.8% and 22.6% of acne prescriptions respectively for 2005 and 2006. The decreasing percentage of acne prescriptions seen from age groups 2 to 4 (refer table 4.12) in both study years, was expected due to a decrease in the prevalence of acne with increased age (Pal, 1997:4, refer to section 2.3.1).

The percentage of isotretinoin prescriptions within the acne prescriptions claimed is revealed in table 4.12. Age group 2 has the highest percentage of isotretinoin prescriptions within the acne prescriptions at 23.8% and 26.6% respectively for 2005 and 2006. This indicated that about a quarter of the identified acne prescriptions, over both study years in the age group 12 to 19 years, contained the drug isotretinoin. And although certain antibiotics also used in treatment of acne were excluded (due to the classification system, refer to section 5.3, limitations) from acne medicine, isotretinoin items were claimed at the highest frequency in age group 2 in both study years (refer to Appendix A, table A3). The position of isotretinoin in each age group in relation to the acne medicine for that specific age group is listed in table A3 in Appendix A.

The percentage of isotretinoin prescriptions in relation to acne prescriptions, increased in all age groups except in age group one over the two year study period (refer to table 4.12). These increases could be due to a variety of reasons, such as an increase in usage of isotretinoin, medical aids only paying for certain acne products, a higher number of severe acne cases occurring or that isotretinoin was prescribed more easily for moderate acne. But this could indicate that, in relation to the other identified acne medicine, isotretinoin was becoming the preferred treatment for acne.

For age group 5, that includes patients older than 35 years, the usage of isotretinoin for acne is lower (11.6% for 2005 and 12.8%for 2006) than for age groups 2, 3 and 4 (exept age group 4 in 2005, with 11.5%) as the age group older than 35 years includes mostly cases of patients suffering from adult acne, medicine induced acne and hormonal changes (menopause in women).

4.7.4 Frequency of acne medicine items claimed according to age groups

The top 5 acne medicine items claimed per age group are listed in appendix A, Table A3 (note - that it only contained acne medicine according to the classification system used for this study). In age group one a topical retinoid, adapalene (Differen®), was claimed at the highest percentage of 15.9% and 18.9% respectively for 2005 and 2006. We have already

noticed that isotretinoin played a lesser role in this age group (as expected), since isotretinoin should not be used in this age group, and therefore isotretinoin claims were in 5th and 7th position in age group 1 (refer to appendix A, table A3).

In age group 2, isotretinoin medicine items were claimed at the highest percentage, at 23.6% and 26.2% of acne medicine items claimed respectively for 2005 and 2006. This further supports the major role isotretinoin played in this specific age group.

In the age groups 3 to 5, isotretinoin medicine items claimed were only second to the oral contraceptive (cyproterone asetate/ethinylestradiol) in number of medicine items claimed over both study years (refer to appendix A, table A3).

This supports the findings that isotretinoin plays a major role in the prescribing patterns and costs of acne in this section of the South African private healthcare sector.

4.7.5 Number of isotretinoin containing prescriptions issued to patients according to age group

Age group 2 received the highest average number of prescriptions per patient per year at 3.16±2.17 and 3.09±2.14 respectively for 2005 and 2006. The average number of prescriptions per patient decreased with an increase in age from age group 2 to age group 5, except for the year 2005 where age group 5 had a slightly higher average number of prescriptions per patient per year than age group 4 (refer to table 14.13). This phenomenon was not further investigated due to reasons already stated in section 4.2.3, indicating that the two one-year periods could be considered too short a time period to present a correct reflection of treatment period with isotretinoin (which should be between 4 and 6 months).

The number of patients for each age group is listed in Table 4.13. Age group 2 also has the largest percentage of isotretinoin patients at 43.4% (n = 2 847) and 44.0% (n = 3 126) in relation to the smallest percentage of isotretinoin patients in age group 1 at 0.69% and 0.37% respectively for 2005 and 2006. Age groups 2 and 3 together (the ages 12 to 27 years) accounted for more than 70% of patiens receiving isotretinoin treatment (refer to table 4.13).

Table 4.13: Average number of prescriptions per patient and the number of isotretinoin users for 2005 and 2006.

Year	Age group	Number of prescriptions	Average number of prescriptions per patient	Number of patients (n)	%*
2005	1	79	1.76 ± 1.54	45	0.7
	2	8 989	3.16 ± 2.17	2 847	43.4
	3	4 969	2.78 ± 2.12	1 787	27.2
	4	1 597	2.40 ± 1.94	665	10.1
	5	2 955	2.43 ± 2.10	1 217	18.6
2006	1	52	2.00 ± 1.96	26	0.4
	2	9 656	3.09 ± 2.14	3 126	44.1
	3	5 645	2.85 ± 2.10	1 979	27.9
	4	1 755	2.67 ± 2.06	657	9.3
	5	3 125	2.39 ± 2.01	1 310	18.5

*Percentage calculated according to the total number of patients per age group for the specific year.

Fleisher *et al.* (2003:665) indicated that a significant proportion (40%) of isotretinoin treatments occurred past the teenage years in the US (refer to section 2.7.2). In comparison, by combining age groups 3, 4 and 5 (including all ages above 19 years), this study indicated that isotretinoin was used in this combined age group by 55.9% and 55.7% of patients, which was higher than the study by Fleisher *et al.* (2003:665) indicated. These identified percentages of the number of patients using isotretinoin correlate with the percentages of the number of isotretinoin prescriptions for these age groups.

4.8 PRESCRIBING PATTERNS OF ISOTRETINOIN ACCORDING TO GENDER

4.8.1 Number of isotretinoin prescriptions according to gender

It was important to divide the prescribing patterns of isotretinoin into gender; to determine whether the side-effect of teratoginicity, which is a major obstacle for this drug (refer to section 2.4.5.2) and only applies to female patients, had an effect on the prescribing patterns of isotretinoin. Therefore it could be expected that more prescriptions could have been claimed for male patients in relation to female patient.

However, female patients received 56.2% (n = 10 450) and 57.4% (n = 11 610) of the total number of isotretinoin prescriptions claimed respectively for 2005 and 2006 (refer to table 4.14). This higher number of isotretinoin prescriptions prescribed to female patients could be

a concern, as more caution should be taken when isotretinoin is prescribed to female patients, especially female patients of child-bearing age.

Table 4.14: Prevalence and average cost of isotretinoin prescriptions for the year 2005 and 2006 according to members' gender

Year	Members' gender	Number of prescriptions (n)	%*	Average cost per prescription (R)	Total cost (R)
2005	Female	10 450	56.2	335.15 ± 209.98	3 502 352
	Male	8 131	43.7	406.36 ± 233.76	3 304 123
	Unspecified	8	0.04	451.99 ± 246.73	3 616
	Total	**18 589**	**100**		**6 810 091**
2006	Female	11 610	57.4	296.36 ± 197.74	3 440 756
	Male	8 609	42.6	358.69 ± 218.29	3 087 923
	Unspecified	13	0.06	252.66 ± 165.65	4 562
	Total	**20 232**	**100**		**6 533 241**

*Percentage was calculated according to the total number of isotretinoin prescriptions for the specific year.

The overall increase of the number of prescriptions for female patients over the two study years was 11.1% (from n = 10 450 in 2005 to n = 11 610 in 2006) and in comparison the male patients had a 5.8% increase (from n = 8 131 in 2005 and n = 8 609 in 2006) (refer to table 4.14). The slightly higher increase seen in the percentages of isotretinoin prescriptions for female patients in relation to male patients over the two study years also constitutes a concern, especially if this could indicate that isotretinoin is being prescribed more easily to female patients.

The percentage of isotretinoin prescriptions to male patients decreased from 43.7% to 42.6% from 2005 to 2006 (refer to table 4.14). This percentage difference in gender did not fully correlate with the study done by Wysowski *et al.,* (2002:507), in the USA, indicating that the male patients received 48% of isotretinoin prescriptions and the female patients 50%.

In relation to this gender difference in isotretinoin prescriptions, the total database indicated that the number of prescriptions claimed was divided into 60.0% for female patients and 39.9% for male patients in 2005 and 59.9% for female patients and 40.0% for males in 2006 (refer to appendix A, table A4). This indicated that the percentage gender difference in isotretinoin prescriptions claimed was in close correlation to the total database.

4.8.2 Average and total cost of isotretinoin prescriptions according to gender

The average costs per isotretinoin prescription for female members were R335.15 ± 209.98 and R296.36 ± 197.74 respectively for 2005 and 2006 (refer to table 4.14). A decrease in the average cost per female isotretinoin prescription of 11.6% (R38.79) was seen over the two study years, which was not practically significant with a d-value of 0.18,. The reason for this decrease, however, could be the increase in generic use already identified (refer to section 4.5.1).

In relation the average costs per male isotretinoin prescription were R406.36 ± 233.76 and R358.69 ± 218.29 respectively for 2005 and 2005 (refer to table 4.14). This also included a decrease in average cost of 11.7% (R47.76) over the study years (the d-value of 0.20, indicating a practical insignificant decrease).

There was a difference of 17.5% in the average cost between female isotretinoin prescriptions and male isotretinoin prescription in both study years. The d-values between the genders were d = 0.30 and d = 0.29 respectively for 2005 and 2006, and were an observable cost difference. This could implicate that higher daily dosages were prescribed for male patients. Reasons for this difference could be the difference in weight between female and male patients and therefore a higher daily dose (mg/kg/day) of isotretinoin would be prescribed to male patients; or male patients could cope better with a higher daily dose and its combined common side effects (which has a higher severity in higher daily doses). The exact reasons are not known.

The total cost of isotretinoin prescriptions only had a relatively small difference between genders at a total cost percentage for isotretinoin prescriptions of 51.4% (n = 3 502 352) and 48.5% (n = 3 304 123) respectively for female and male prescriptions in 2005, in relation to 52.7% (n = 3 440 756) and 47.3% (n = 3 087 923) respectively for female and male prescriptions in 2006 (refer to table 4.14).

4.8.3 Number of isotretinoin containing prescriptions issued to patients according to gender

Female patients claimed an average of 2.83 ± 2.13 prescriptions in the year 2005 and an average of 2.85 ± 2.14 prescriptions in 2006. In relation to this the male patients received a slightly higher average number of prescriptions per male patient at 2.98 ± 2.23 and 3.02 ± 2.17 prescriptions respectively for 2005 and 2006 (refer to table 4.15). This indicated that according to averages (including standard deviation) an expected treatment period was

slightly longer for male patients than for female patients. This occurence was, however, not further investigated due to reasons already stated in section 4.2.3 and 4.7.5, which are related to the short time period of this study.

Table 4.15: Number of prescriptions per patient and the number of patients according to gender for 2005 and 2006.

Year	Member gender	Number of prescriptions	Average number of isotretinoin prescriptions per patient	Number of patients (n)	%*
2005	Female	10 450	2.83 ± 2.13	3 692	57.5
	Male	8 131	2.98 ± 2.23	2 729	42.5
	Unspecified	8	1.33 ± 0.52	6	0.09
2006	Female	11 610	2.85 ± 2.14	4 074	58.8
	Male	8 609	3.02 ± 2.17	2 849	41.1
	Unspecified	13	3.25 ± 1.50	4	0.06

*Percentage was calculated according to the total number of patients using isotretinoin for the specific year.

The percentage number of female patients using isotretinoin for the year 2005 was 57.5% (n = 3 692) in relation to 42.5% (n = 2 729) male patients (refer to table 4.15). For the year 2006 the percentage number of female patients was slightly higher at 58.8% and male patients slightly lower at 41.1% (refer to table 4.15). This gender difference in isotretinoin use was slightly larger than the ratio of the different genders on the total database at 55.5% female patients and 44.4% male patients over both the study years (refer to Appendix A, table A5) and also indicated a slightly larger difference in both study years than a study done by Wessels *et al.* (1999:787), also in South Africa, indicating that of the patients using isotretinoin, 45% were male and 55% were female (refer to section 2.7.1 in literature review). The differences in percentage of patients using isotretinoin differed from the equally distributed use if isotretinoin in the US, which could be due to their strict programmes on isotretinoin use in female patients (Wysowski *et al.*, 2002:507; Asoulay *et al.*, 2006:670, refer to section 2.7.1).

4.8.4 Frequency of acne medicine items prescribed and claimed according to gender *in relation to isotretinoin*

About 75% of acne prescriptions (83 492 in 2005 and 81 163 in 2006) was prescribed to female patients and only 25% (28 009 in 2005 and 26 550 in 2006) was prescribed to male patients. The high number of acne medicine prescriptions for female patients could be due to the effect oral contraceptives (hormone therapy for acne, only in females) have on the number of female prescriptions containing acne medicine (discussed in next paragraph) or the higher number of acne visits by female patients (Stern, 2000:1045; Fleischer *et al.*, 2003:664, refer to section 2.7.1).

The frequency of the identified acne medicine according to active ingredient in the different genders is indicated in appendix A, table A6. The highest frequency of acne medicine claimed for female patients in both study years indicated the oral contraception which represented 42.0% (n = 39 862) and 41.7% (n = 38 681) of the acne medicine items claimed respectively for 2005 and 2006 (refer to table A6). This was followed by isotretinoin medicine items at 12.7% (n = 12 081) and 14.5% (n = 13 457) respectively in 2005 and 2006. These two acne medicine ingredients made up more than 50% of the acne medicine items claimed for female patients in this section of the private health care sector of South Africa (refer to appendix A, table A6). The topical retinoid, adapalene, had the third highest frequency in both study years at 7.3% (n = 6 953) and 7.6% (n = 7 076) respectively for 2005 and 2006 (refer to table A6).

In comparison to this, the highest frequency over both study years for acne medicine items claimed for male patients indicated isotretinoin at 29.2% (n = 9 543) and 32.2% (n = 10 062) respectively for 2005 and 2006. The topical retinoid was claimed at the second highest frequency at 11.8% and 12.9% respectively for 2005 and 2006. The third position belonged to different drugs in 2005 (Methylprednisolone/Neomycin) and 2006 (Minocycline) (refer to appendix A, table A6). Oral contraceptives did not play a part in male patients and therefore it could only be identified in the frequency of acne medicine in female patients.

Other identified acne medicines claimed, those with a frequency of more than 3%, are listed in Appendix A, table A6.

Interesting is that more systemic isotretinon items were claimed than topical retinoids (including adapalene, tretinoin and topical isotretinoin) in both female and male patients. The combined number (male and female) was

- 20 923 systemic isotretinoin items claimed in relation to 16 479 topical retinoids in 2005; and
- 22 646 systemic isotretinoin items claimed in relation to 17 249 topical retinoids in 2006.

This occurred even though the global alliance recommended that topical retinoids should be the primary treatment for most forms of acne (the foundation of treatment), and systemic isotretinoin only be used in severe cases of acne (Gollnick et al., 2003:S9, refer to section 2.3.6.2). This higher number of systemic isotretinoin items claimed in relation to topical retinoinds could indicate that systemic isotretinoin was preferred to topical retinoids by prescribers. Systemic isotretinoin is known to be more effective but should not be used as first-line treatment. The exact reasons for the higher number of systemic isotretinoin use are not known (fell outside the scope of this study) and the exact diagnoses for the use of isotretinoin are not known (refer to limitations, section 5.3). It should be noted that systemic isotretinoin was claimed and used at a higher prevalence than the topical retinoids and therefore it could indicate that the prescribers prefer to prescribe systemic isotretinoin items to topical retinoids in this section of the private health care sector of South Africa.

For both male and female patients adapalene was the topical retinoid prescribed at the highest percentage, followed by tretinoin (refer to Apendix A, table A6) and then the small portion of isotretinoin products indicated as a topical retinoid, in the form of topical isotretinoin (Isotrex® gel, refer to table 4.5). Reasons for this could be that less skin irritation is experienced by patients using the other topical retinoids (especially adapalene) than with topical isotretinoin(Io Annides *et al.*, 2002:526, refer to section 2.6).

4.9 PRESCRIPTIONS CONTAINING ISOTRETINOIN ACCORDING TO AGE AND GENDER GROUPS

The median age of isotretinoin users identified was 21 years for female patients and 18 years for male patients in both the study years. This median was lower than a study done by Wessels *et al.* (1999:787) in the late nineties, also in South Africa, which indicated a median of 25 and 19 years respectively for female and male patients using isotretinoin. The biggest difference was the decrease in age of female patients indicating that isotretinoin use is more prevalent in a younger age than almost a decade ago.

The number of prescriptions per patient according to gender can be seen in table 4.16. In all the age groups the female patients claimed a higher percentage of prescriptions in relation to

the male patients except in age group 2 (12 to 19 years), where male patients received 27.8% and 27.5% of isotretinoin prescriptions respectively in 2005 and 2006 in comparison to female patients of only 20.5% and 20.2% over the same time period (refer to table 4.16). This indicates that isotretinoin was more likely to be prescribed to male patients in age group 2 (12 to 19 years) than in all the other age groups where isotretinoin was prescribed mainly to female patients.

Age group 2 (12 to 19 years) contained 63.6% and 64.6% of male isotretinoin prescriptions respectively for 2005 and 2006. This was in close relation to a study done by Wysowski *et al.* (2002), in the USA, indicating that 63% of males prescribed isotretinoin were aged 15 to 19 years (refer to section 2.7.2).

In comparison age group 2 (12 to 19 years) only represented 36.5% and 35.2% of female isotretinoin prescriptions respectively for 2005 and 2006. If the female age groups 2 and 3 were combined (ages 12 to 27 years) a similar percentage, 66.4% and 66.7% of isotretinoin prescriptions respectively for 2005 and 2006 are seen.

Table 4.16: Number of isotretinoin prescriptions in the age groups and gender combined for 2005 and 2006.

Age group	Gender	Number of prescriptions for 2005	%*	Number of prescriptions for 2006	%*
1	Female	46	0.25	36	0.18
	Male	33	0.18	16	0.08
2	Female	3 814	20.5	4 092	20.2
	Male	5 170	27.8	5 559	27.5
3	Female	3 128	16.8	3 657	18.1
	Male	1 839	9.9	1 980	9.8
4	Female	1 244	6.7	1 376	6.8
	Male	353	1.9	379	1.9
5	Female	2 218	11.9	2 449	12.1
	Male	736	4.0	676	3.3
	Unspecified	8	0.04	13	0.06
	Total	**18 589**	**100**	**20 233**	**100**

*Percentage was calculated according to the total number of isotretinoin prescriptions for the specific year.

According to a recent population-based study done by Bernard *et al.* (2006:200), in Canada, including 8 609 women of child-bearing potential, it was indicated that 210 pregnancies occurred while these patients were using isotretinoin (very similar guidelines were applied as used in South Africa); 2.4% of female patients of child-bearing age were in danger of the teratoginicity effect of isotretinoin (refer to section 2.7.1.1). This percentage could be used in a scenario to calculate the possible pregnancies that may occur while female patients are using isotretinoin (i.e. in this section of the private health care sector of South Africa).

If only the female patients in age groups 2, 3 and 4 (ages 12 to 35 years) are classified as *woman of child-bearing potential for this scenario, then the number of prescriptions for this* combined age group for females would be 8 186 and 9 125 respectively for 2005 and 2006 (*refer to table 4.16*).

The average number of isotretinoin prescriptions for female patients presented as 2.83 and 2.85 respectively for 2005 and 2006 (refer to table 4.15, standard deviation not taken into account). This indicates that an estimated number of

- 2 892 (2005) and
- 3 201 (2006)

female patients of child-bearing potential could be identified using isotretinoin treatment.

If the study done by Bernard *et al.,* (2006:200) is applied to this number of female patients of *child-bearing potential (2.4%), it could indicate that a possible*

- 69 (2005) and
- 77 (2006)

unwanted pregnancies could occur, if guidelines were not followed correctly to ensure that pregnancies would not occur. This is the reason why the high number of female users of isotretinoin in the child-bearing age is a concern and the need to do further studies on the pregnancy prevalence of female patients using isotretinoin in South Africa is important. Such studies could indicate whether it would be necessary to implement a stricter prescribing programmes (as incorporated in the USA – namely IPLEDGE, refer to section 2.4.5.2 and 2.7.1.1) *to prevent such pregnancies from occurring in the Republic of South Africa.*

4.10 MEDICINE ITEMS PRESCRIBED AND CLAIMED IN COMBINATION WITH ISOTRETINOIN PRODUCTS

The database contained over 2600 and 2900 different combinations of medicine items combined with isotretinoin products respectively for 2005 and 2006, indicating that a variety of medicine items had been prescribed and claimed in combination with isotretinoin. According to the prescriptions that were claimed, the combinations varied from a single medicine item combined with isotretinoin products to the addition of up to nine different medicine items claimed in combination with the isotretinoin products.

Combinations were identified of the different products of isotretinoin with different medicine items (according to trade names). This indicates that, for examle Roaccutane® 20mg was prescribed and claimed in combination with Minerva® and on another prescription claimed the combination of Roaccutane® 20mg with Ginette® (containing the same active ingredient, only a different generic) occurred but was indicated as a different combination. The same would occur if the combined medicine item/s were the same, but the isotretinoin products differed.

Only combinations with a prevalence of more than 0.1% were taken into consideration and therefore not all combinations were used for analyses. This section is only an illustration of certain combinations of isotretinoin with other medicine items. The tables containing the frequencies of combination medicine with isotretinoin are available in Appendix A, table A7.1 and table A7.2.

The focus of this study was only on combinations occurring on the same prescription and not all medicine items prescrbed to a specific patient. Therefore concurrent use of other medicine or supplements with isotretinoin could not be identified for this study (refer to limitations in section 5.4).

4.10.1 Prescriptions of isotretinoin products without combinations

The total number of prescriptions containing isotretinoin products has already been determined (refer to section 4.5.2). Of this total number of isotretinoin prescriptions, systemic isotretinoin on its own (indicating that no other medicine item was prescribed and claimed in combination) was claimed in 70.8% and 69.3% of prescriptions respectively in 2005 and 2006 (refer to appendix A, table A7.1 and A7.2). This was lower than in the study done by Wysowski *et al.,* (2002:507), indicating that 91% of times isotretinoin was prescribed alone in the USA (refer to section 2.7.4). This indicates that South African prescribers could be more

in favour of prescribing other medicine in combination with isotretinoin. Reasons for this are unknown, although it was thought to be either to facilitate in managing of side-effects or to have a synergistic effect if combined with isotretinoin (this was not always supported by specific clinical studies).

The isotretinoin 20mg capsules claimed alone, took up the first three positions in the frequency table over both years where Roaccutane® 20mg was claimed at the highest frequency in 2005 and Acnetane® 20mg in 2006 (refer to appendix A, table A7.1 and table A7.2).

Although the combination of the two different dosage strengths of isotretinoin has already been discussed in section 4.5.3, these results (refer to appendix A, table A7.1 and table A7.2) indicated prescriptions claimed where the combination of the different isotretinoin strengths occurred alone on a prescription and claim. For the year 2005 the combination of Roaccutane® 10mg capsules with Roaccutane® 20mg represented the highest claimed combination of isotretinoin prescribed alone and the combination of Acnetane® 10mg and 20mg capsules featured in 2006 (refer to appendix A, table A7.1 and table A7.2). This correlated with the combination study done in section 4.5.3, which indicated all prescriptions containing the different strenghts of systemic isotretinoin.

The frequency of only 10mg isotretinoin capsules occurring per prescription (position 5, 8 and 9 in 2005 and position 6, 8 and 9 in 2006) could indicate patients using low dose therapy (refer to section 2.7.5). Such low dose therapy prescribed and claimed alone occurred in 9.4% and 9.1% of isotretinoin prescriptions claimed respectively for 2005 and 2006. Reasons for this occurrence could either be that higher dosages were intolerable to these patients and the daily dosage was then decreased to manage the side-effects (Gibbon *ed.*, 2005:194) or a low dosage regimen was followed from the start (refer to section 2.4.4 and 2.7.5).

The topical form of isotretinoin, Isotrex® gel, was only prescribed and claimed alone on 159 and 161 occasions respectively for 2005 and 2006 (position 10 in both years, refer to appendix A, table A7.1 and A7.2). This indicated that out of the total number of Isotrex® gel items, it was only prescribed alone in 22.4% and 18.2% of prescriptions claimed, indicating that it was preferred to combine this topical form of isotretinoin with other medicine items. For combinations identified, in table A7.1 and A7.2, with topical isotretinoin refer to section 4.10.3.

4.10.2 Combinations with oral contraceptives

The first combination with a medicine item other than isotretinoin was the combination of Roaccutane® 20mg capsules with Minerva®, occurring in position 11 in both years (refer to appendix A, table 7.1 and table 7.2). Minerva® is a hormone tablet containing cyproterone/ethinylestradiol indicated for androgen depended acne and is used as an oral contraceptive (Gibbon *ed.,* 2005:222). This was an interesting combination since both medicine items (Minerva® and Roaccutane®) are indicated for acne treatment. The contraceptive indication of Minerva® is also of use to prevent the occurrence of pregnancy and therefore preventing the teratogenicity effect of isotretinoin from occurring. The main reason for this combination is thus thought to be for the contraception indication of Minerva®. Isotretinoin is already a highly effective treatment for severe acne and no specific clinical studies in the litrature were found to contain indications that the combination of cyproterone/ethinylestradiol with systemic isotretinoin enhances the effectiveness of isotretinoin or the recovering from acne (Gollnick *et al.,* 2003;S25, refer to section 2.3.6.3). A study done by Marsden *et al.* (1984:697) indicated that the combined use of cyproterone (not in combination with ethinylestradiol) and systemic isotretinoin in male patients had no enhanced effect on the effectiveness of systemic isotretinoin. Further studies could be necessary to evaluate the effectiveness of cyproterone/ethinylestradiol in combination with systemic isotretinoin.

There are different trade names for products containing cyproterone/ehinylestradiol, namely Minerava®, Diane-35® (the innovator) and Ginette®. The combination of isotretinoin with these products occurred relatively frequently in table A7.1 and A7.2, in position 11, 13, 14, 18, 29, 31 and 33 in the year 2005 and in position 11, 12, 13, 24, 28 and 41 in the year 2006. The only other oral contraceptive occurring in the frequency tables was Yasmin®, containing drospirenone/ethinyloestradiol (main indication for contraception, but could also be used in acne). Yasmin® occurred in position 23 and 24 in 2005 and in position 16 and 21 in 2006 (refer to appendix A, table A7.1 and table A7.2).

In the total number of combinations, oral contraceptives occurred on the same prescription claim in combination with isotretinoin, in 4.8% (898 prescriptions) and 5.3% (1 065 prescriptions) of prescriptions respectively for 2005 and 2006. This was higher than any other medicine group identified in the total number of combinations. This indicated that only 8.6% and 9.2% of prescriptions claimed for female patients had oral contraceptives prescribed concurrently. This percentage was lower than the study done by Wessels *et al.*, (1999:788) in the late nineties in South Africa, which indicated that 14.4% of female patients receiving isotretinoin were co-prescribed an oral contraception (refer to section 2.7.4). This

low percentage of co-prescribed oral contraceptives could be a concern if this would indicate that prescribers were less strict on using at least two different contraception methods to prevent pregnancy in potential sexually active female patients of child-bearing age as the guidelines suggest (Sinclair & Jordaan, 2005:889, refer to section 2.7.1.1).

Through this identification of co-prescribed contraceptives it could be necessary to do further investigations/studies on the number of female patients using contraceptives in combination with their isotretinoin treatment and also whether guidelines are adhered to, especially in female patients of childbearing potential (already identified in section 4.9).

4.10.3 Combinations with antibiotics

Antibiotics are important medicine products used in the treatment of acne (refer to section 2.3.6.1), although not much is known about antibiotics combined with systemic isotretinoin. There were a number of combinations with isotretinoin and antibiotics, especially with Purbac®, containing the combination active ingredients trimethoprim and sulphamethoxazole (co-trimoxazole). The possible clinical reason for this combination is thought to be that Purbac® has an antimicrobial effect (on *P. acnes*) and therefore supports the moderate (indirect) antimicrobial effect isotretinoin has on *P. acnes* (Gollnick et al., 2003:1590; Leyden, 2003:S202, refer to section 2.3.6, table 2.3). No specific clinical studies could be identified to support the combination of co-trimoxazole with systemic isotretinoin to indicate that such combinations would enhance the effect of isotretinoin.

In the year 2005 the combination of a systemic isotretinoin product with Purbac® occurred in position 12, 26 and 34 and in position 17, 18, 30 and 43 in 2006 (refer to appendix A, table A7.1 and table A7.2). It was noted that the isotretinoin combinations with Purbac® had a lower average cost when compared to the average cost of the specific isotretinoin product prescribed alone, (taken from table A7.1). For example, the analysis showed that Roaccutane® 20mg capsules alone had an average cost of R493.42 ± 229.65 compared to the combination of Roaccutane® 20mg with Purbac® at an average cost of R216.35 ± 183.69. The d-value of this example is 1.21, indicating that there is a practically significant cost difference in this example. The average cost was lower in all cases of Purbac® combined with systemic isotretinoin, which occurred in table A7.1 and in table A7.2 (refer to appendix A), all with practical significant or observable (may be significant) differences (d-values of more than 0.8 and 0.5).

This occurrence may indicate that if the combination of Purbac® together with systemic isotretinoin would be prescribed and claimed in combination, the lower average cost of this combination could be the result of a lower dose of systemic isotretinoin prescribed. This phenomenon could not be investigated. Further studies on these combinations and how efficient they are would be necessary, especially if this could indicate that the cost of isotretinoin in combination with Purbac® (or other systemic antibiotics) would ensure lower costs and as a result costs could be saved, but without sacrificing the desired results.

The other combination of systemic isotretinoin with a systemic antibiotic identified in the top 0.1% of combinations, was with Adco-erythromycin® (also used in acne, refer to section 2.3.6.1), occurring in position 22 in table A7.1 (refer to appendix A). A lower average cost was also indicated for this combination (d-value of 0.55) in relation to that specific isotretinoin product prescribed alone. Other combinations occurring between systemic isotretinoin and systemic antibiotics were not investigated, due to an occurrence of less than 0.1%.

The topical form of isotretinoin (Isotrex® gel) was also combined with Purbac® in position 33 in table A7.2 for the year 2006. This is a proposed combination where a topical retinoid with a systemic antibiotic is combined (Leyden, 2003:S208, refer to section 2.3.6.2). The topical form of isotretinoin (Isotrex gel®) also occurred in combination with other systemic antibiotics in table A7.1 and A7.2, namely Tetralysal® or Cyclimycin®. This occurred in position 20 (Tetralysal®) and 32 (Cyclimycin®) in the year 2005 and in position 14 (Tetralysal®) in the year 2006. Tetralysal® (containing lymecycline) and Cyclimycin® (containing minocycline) are both tetracyclines indicated for the treatment of acne; both recommended in combination therapy (Leyden, 2003:S208, refer to section 2.3.6.2).

The only other time Isotrex gel® occurred in combination, on more than 0.1% of combination prescriptions, was with a topical antibiotic, namely Zineryt® (containing erythromycin and zinc acetate) in position 40 in table A7.2, in the year 2006. Zineryt® is indicated for moderate to severe acne.

The combination of systemic isotretinoin products combined with a topical antibiotics also occurred with Fucidin® cream (position 30, table A7.1), containing the active ingredient fusidate for the treatment of staphylococcal skin infections, and Zineryt® (position 31, table A7.3).

4.10.4 Combinations with tear replacements

The combination of Tears naturale II®, Teargel® or Refresh® (all are tear replacements, Gibbon *ed.*, 2005:521) with systemic isotretinoin occurred in a number of occasions. In 2005 the combination of systemic isotretinoin with one of these tear replacements occurred in position 15, 16, 17, 19, 25, 27, 28 and 38 and for 2006 this occurred in position 20, 22, 23, 32, 34, and 35 (refer to appendix A, table A7.1 and table A7.2). These combinations most likely occurred due to one of the common side-effects of isotretinoin, namely dry eyes/conjunctivitis, presenting in almost half of the patients using systemic isotretinoin (McLane, 2001:S192-S193; Presbury *et al.*, 1997:1412, refer to section 2.4.5.1, table 2.4).

The average cost of these specific combinations was also higher than the average cost of these specific isotretinoin products prescribed alone. This indicates that extra costs are involved in the treatment of the side-effects of isotretinoin. The evaluation of additional costs surrounding isotretinoin side-effects fell outside the scope of the study.

Tear replacements occurred in combination with isotretinoin in 3.5% (in 658 prescriptions) and 2.4% (in 487 prescriptions) of all prescription claims respectively for 2005 and 2006.

Combinations with products to facilitate the other common side-effects of isotretinoin, e.g. dry lips and skin, nose bleeds, joint and muscle pain, etc. (McLane, 2001:S192-S193; Presbury *et al.*, 1997:1412, refer to section 2.4.5.1, table 2.4) were not identified.

4.10.5 Combinations with topical retinoids

The combination of systemic isotretinoin with a topical retinoid occurred on a frequent basis in table A7.1 and table A7.2. Differin® cream/gel (containing adapalene) combined with systemic isotretinoin occurred in positions 21, 35 and 37 in the year 2005 and in the positions 25, 26, 29, 36 and 42 in 2005. The only other combination with a topical retinoid occurred with Ilotycin-A® cream (containing tretinoin) in position 39 in table A7.2 (refer to appendix A).

Although topical retinoids are not contraindicated with systemic isotretinoin (including topical tretinoin, only systemic tretinion is contraindicated, refer to section 2.4.7), the use of these combinations are not well-known. The results indicate that combined prescribing does occur. It is, however, well-known to use topical retinoids after systemic isotretinoin treatment as maintenance therapy (Leyden, 2003:S208, refer to section 2.3.6.4, figure 2.7).

The average cost of the combination of a systemic isotretinoin product with a topical retinoid had no specific pattern in relation to that specific systemic isotretinoin product claimed alone, indicating that some combinations had a higher average cost and others a lower average cost. The only combination indicating a practical significant cost difference applied to Acnetane® 10mg combined with Differin® cream (position 25, table A7.2) which indicated an average cost of R248.41±42.03 in relation to Acnetane® 10mg alone with an average cost of R114.36±55.76 with a d-value of 2.40 and Acnetane® 20mg combined with Differen® gel (position 35, table A7.1) which indicated an average cost of R566.20 ± 172.09 in relation to Acnetane® 20mg alone at an average cost of R355.77 ± 152.83, with a d-value of 1.22 . In position 21 (refer to table A 7.1) and position 36 (refer to table A7.2) the average cost of the combinations was lower than the average cost of the systemic isotretinoin product alone, indicating the systemic isotretinoin product could have been prescribed in a low daily dose (there was no practical significant cost difference). These identified combinations do not indicate whether the combination of topical isotretinoin with systemic isotretinoin was cost saving. Further studies on the combination of systemic isotretinoin with topical retinoids are necessary to investigate the value of such a combination.

Combinations of systemic isotretinoin with a topical retinoid occurred in 2.5% (458 claims) and 3.1% (625 claims) of prescription claims. Although this occured in a low percentage of prescriptions, an increase in combined prescribing of a topical retinoid with systemic isotretinoin was observed. Studies on the combined prescribing could also be necessary to investigate whether the patients' skin could tolerate both a systemic and topical retinoid in combined use, since skin irritation is a side-effect of both these medicine items (Gibbon *ed.*, 2005:193-195).

4.10.6 Combinations with corticosteroids

Combinations with corticosteroids occurred in both frequency tables. The combination of a systemic corticosteroid, namely Be-Tabs Prednisone® or Panafcort® (both containing prednisone), with a systemic isotretinoin product occurred in position 36 in 2005 and position 15, 19 and 38 in the year 2006. The reason for these combinations is thought to be for the acne flare-ups some patients experience with systemic isotretinoin treatment. Caution should be exercised when systemic corticosteroids are prescribed with systemic isotretinoin. Systemic corticosteroids are known to cause osteoporosis and no formal clinical studies have been conducted to assess whether there could be an interactive effect on bone loss between systemic corticosteroids and systemic isotretinoin (Drug Library, 2008).

In position 37 (table A 7.2) is the combination of systemic isotretinoin with a topical corticosteroid. The reason for this combination should be the same as for systemic corticosteroids. The average cost of these combinations is presented in table A7.1 and table A7.2 (refer to appendix A), indicating either higher or lower average costs of these combinations in comparison to the specific isotretinoin product prescribed alone.

4.10.7 Prevalence of drug interactions identified with systemic isotretinoin

The only other drug combination, indicated in table A7.1 and table A7.2, not discussed is the combination of Benzac AC 5® gel (containing benzoyl peroxide) with Acnetane® 10mg in position 27 of table A7.2. Benzoyl peroxide (only in topical form) is also used in the treatment of acne, and although it is not an antibiotic it has an antimicrobial effect (Gollnick et al., 2003:1590; Leyden, 2003:S202, refer to section 2.3.6, table 2.3). Benzac AC 5® is not recommended for concurrent use with systemic isotretinoin. Bensoyl peroxide has a drying effect and because systemic isotretinoin also has a drying effect the concurrent use of these medicine items is not recommended (Gibbon *ed.,* 2005:194, refer to section 2.4.7).

However, the real problematic drug interactions of isotretinoin are with vitamin A, acitretin and tretinoin (systemic). This combined use could cause hypervitaminosis A (toxicity). The other potential problematic drug interaction could be the combination of systemic isotretinoin with systemic tetracyclines, both of which have been associated with benign intracranial hypertension. (For drug interactions refer to section 2.4.7).

When including all combinations claimed there were only one combination of vitamin A (Arovit®) and systemic isotretinoin identified over both study years and none with the other products which could cause toxicity, hypervitaminosis A.

In 139 (0.75%) and 130 (0.64%) prescriptions a systemic tetracycline (including doxycicline, minocycline, lymecycline and oxytetracycline) was claimed in combination with systemic isotretinoin respectively for 2005 and 2006, even though a potential drug interaction is known for such combined usage. It is not known whether any cases of benign intracranial hypertension did occur or were identified, but such combined prescribing should be addressed as a concern.

4.10.8 Extra costs of the combination products with isotretinoin

Over all, the isotretinoin and the combination medicine items prescribed on the same prescription for all combinations had a sum total of R7 651 856 and R7 538 658 respectively for 2005 and 2006. This indicated that the medicine items prescribed and claimed in combination with isotretinoin had a total cost of R841 766 (in 2005) and R1 005 417 (in 2006). This is an indication that extra costs were involved with isotretinoin treatment, increasing the burden isotretinoin treatment cost has on a medical scheme.

4.11 CHAPTER SUMMARY

In this chapter the results were given and discussed. The prescribing patterns of isotretinoin products including cost analyses were looked at. This was done for the different prescribers, age groups, gender and the combinations of medicine items prescribed and claimed with isotretinoin products. The conclusions follow in the next chapter.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

Conclusions were drawn from the literature review and empirical results. The recommendations derived from the study on the prescribing patterns of isotretinoin will be discussed. Limitations of the study are also discussed in the last section of this chapter.

5.1 CONCLUSIONS

In order to ensure the set aims were achieved, the conclusions drawn with regard to each specific research objective will be discussed briefly:

5.1.1 Literature objectives:

- *The first specific aim was to present a brief overview of the anatomy of the skin, with reference to the pilosebaceous unit.*

A brief overview was given on the anatomy of the skin. Illustrations and short discussions were used to describe the different skin layers and their functions. The pilosebaceous unit was discussed with the focus on the sebaceous gland and its function in acne. A description of the anatomy of the skin and especially the pilosebaceous unit was important because it harbours the origin of the relevant disease, called acne. (Refer to section 2.1 and 2.2)

- *The second specific aim was to review acne as a disease and the treatments available.*

Acne is a highly prevalent disease, affecting most people at some stage, although to different degrees. Acne has the highest prevalence in adolescents and usually thereafter decreases with increased age (Pal, 1997:4). The known pathogenesis of acne was investigated although much is still unknown about the disease development. Acne grading systems were

used to indicate the severity of acne although there is room for improvement of acne grading systems. Acne has a lasting effect on some patients through the development of acne scars. The different kinds of acne scars were identified and this indicated the need to act quickly with successful acne treatment to prevent acne scarring from occurring. Acne affects the quality of life and patients suffering from severe acne lose approximately 15% of their physical and psychological quality of life, emphasising the importance of a successful treatment for patients suffering from this embarrassing disease (Jordan *et al.*, 2005:191). The different acne treatments were identified (with the exception of systemic isotretinoin). The identified treatments were the antibiotics, topical retinoids and hormonal treatment, together with the importance of combination therapy. (Refer to section 2.3)

- *The third specific aim was to present an overview (including indications, dosages, adverse effects and interactions) of isotretinoin treatment through available literature.*

The revolutionary drug, isotretinoin, is discussed on the different aspects known. Isotretinoin is the only acne treatment that has an effect on all the pathophysiological factors of acne although the exact mechanism of action is not fully known. The indications for isotretinoin in acne were identified. It was also identified that a decline in isotretinoin treatment for severe acne and an incline in its use for mild to moderate acne could occur. The optimum dosage regimen was identified indicating that a total cumulative dose of 120 to 150 mg/kg should be reached to ensure that a success rate of about 90% could be achieved (Wessels *et al.*, 1999:784; Kaymak & Ilter, 2006:580). (Refer to section 2.4)

The adverse effects of isotretinion were discussed including the common side-effects and the problematic side-effects of teratogenicity (the major obstacle for this drug), liver and blood effects, and depression (consensus still pending). The rate of recurrence of acne after treatment with isotretinoin was also mentioned. The known drug interactions were identified, with the major drug interactions with vitamin A, acitretin and tretinoin that could result in hypervitaminosis A; and tetracyclines that should be avoided because both agents have been associated with benign intracranial hypertension (FDA, 2005; Gibbon *et al.*, 2005:194; Hanson & Leacman, 2001:177). The high success rate of isotretinoin indicates that this product has a positive effect on the quality of life in patients suffering from acne (Jorden *et al.*, 2005:191). (Refer to section 2.4 and 2.5)

The effectiveness of the topical form of isotretinoin does not compare with the systemic form of isotretinoin. It is suggested to rather use adapalene in place of topical isotretinoin as it has

the same effectiveness, but less skin irritation (Io Annides *et al.*, 2002:526). (Refer to section 2.6)

- *The fourth specific aim was to investigate different aspects (including age, gender and prescribers) of isotretinoin treatment through available literature.*

The use of isotretinoin is increasing, emphasising the importance to identify the aspects of isotretinoin prescribing. The difference in isotretinoin use according to gender has been tabled through different available studies (Wysowski *et al.*, 2002:507; Asoulay *et al.*, 2006:670; Wessels *et al.*, 1999:787). The use of isotretinoin in female patients of child-bearing potential is a major concern and the correct management of isotretinoin in these patients is of utmost importance. The US has incorporated a very strict managing programme (called iPLEDGE –the largest risk-minimisation programme ever been implemented for a drug) to manage the use of isotretinoin and hopefully prevent pregnancies from occurring while female patients are using isotretinoin treatment (Honein et al., 2007:7-11). (Refer to section 2.7)

Adolescent patients are most frequently prescribed isotretinoin, together with the indication that the majority of women using isotretinoin are of a relatively higher age than the men (Wysowski *et al.*, 2002:507; Fleischer *et al.,* 2003:663; Stern, 2000:1047). Dermatologists prescribed the majority of isotretinion prescriptions in the USA and in some identified countries they have sole authority to prescribe isotretinoin. Isotretinoin was prescribed mostly alone on a prescription, although a variety combined medicine use was also observed (Wysowski *et al.,* 2002:507; Wessels *et al.*, 1999:788). The different dosage regimes tried and tested were identified. Most dosage regimes were effective, indicating that a different dosage regimen could be implemented although further studies need to be done, especially if the use of this successful drug would be shifted to milder forms of acne.(Refer to section 2.7.2 to 2.7.5)

The introduction of generic products for isotretinoin at the end of 2002 led to a decrease in the usage of the original product. Isotretinoin became more affordable and therefore it could become more acceptable to prescribe isotretinoin to patients (Koren *et al.*, 2004:1567; Honein *et al.*, 2004:1075). The different influences in isotretinoin prescribing including previously mentioned influences were discussed. (Refer to section 2.7.6 and 2.7.7)

Acne cost plays a major role in dermatological costs and isotretinoin is known as an expensive treatment regimen for acne, although isotretinoin was identified as cost-effective in

the treatment of severe acne (Wessels *et al.*, 1999;785). Acne and especially isotretinoin treatment will continue to be a major expense to the funders of health. (Refer to section 2.7.8)

- *The fifth aim was to mention briefly what managed heathcare, including drug utilisation review, pharmacoepidemiology and pharmacoeconomics, consist of.*

Managed healthcare would include any kind of health care service which are paid for, all or in part by a third party. This includes any government entity and for which the focus of any part of clinical decision making is other than between the practitioner and the client or patient (Cohen, 2003:34). The advantages of managed healthcare were identified including the South African perspective of managed healthcare.

Drug utilisation review has a principal aim to facilitate rational use of drugs in the population and it forms part of investigational studies. Important for this study is the retrospective drug utilisation review that evaluates drug prescribing; dispensing and/or patient use after the drug has been dispensed, in a given healthcare environment against predetermined agreed upon criteria and standards (Blackburn *et al.*, 2001:7).

Pharmacoepidemiology is defined as the study of the use and effects or side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs and improving health outcomes (Sjöqvist & Birkett, 2003:77).

Pharmacoeconomics include the description and analysis of the cost of drug therapy to a healthcare system and society. It provides measures and compares the cost and consequences of pharmacoeconomical products and services (Bootman *et al.*, 1991:4). The economical aspects of medical interventions are becoming more important because of healthcare expenditure that is increasing dramatically. For this reason there is a worldwide recognition of the need to control the rising cost of healthcare (Ellis *et al.*, 2002:271; Jessop *et al.*, 2002;568). (Refer to section 2.8)

5.1.2 Empirical objectives:

- *The sixth specific aim was to determine the prescribing patterns including aspects of cost of isotretinoin products with comparisons to acne products and the total claimed medicine items in a section of the private healthcare sector of South Africa.*

It was found that isotretinoin containing prescriptions represented 0.22% (N = 18 589 in 2005 and N = 20 232 in 2006) of the total prescriptions claimed in both study years and represented 16.7% and 18.8% of acne prescriptions claimed respectively for 2005 and 2006 (refer to section 4.2.3, table 4.1). A total number of 38 821 isotretinoin containing prescriptions was observed (refer to table 4.1).

Isotretinoin products indicated a higher increase in claims of 8.8% (including the number of patients (7.8%)) in comparison to the increase identified in all medicine products and the decrease observed for all the identified acne products claimed through the database. This indicated that an increased use was noted over the two study years in this section of the private healthcare sector of South Africa (refer to section 4.2.3 and 4.2.4).

A decrease in average cost of isotretinoin prescriptions was noted (R366.35 ± 223.52 to R322.92 ± 223.52) over the two study years (refer to section 4.3.1, table 4.3.3). This is a positive shift towards the goal of providing medicine at an affordable price.

It was found that isotretinoin treatment played the biggest role in acne medicine costs when compared to any other single acne medicine treatment identified in both study years (refer to section 4.3.2 and table A1.2 in Appendix A). In relation to all medicine products claimed isotretinoin products were identified as an expensive medicine product (refer to section 4.3.2). Isotretinoin treatment cost had a burden to funders estimated at R56 000 and R52 000 per 10 000 beneficiaries respectively for 2005 and 2006 (refer to section 4.3.2).

The topical form of isotretinoin (Isotrex® Gel) represented a relatively low percentage of the isotretinoin prescriptions, representing only 3.3% and 3.8% of isotretinoin containing prescriptions in comparison to 96.7% and 96.2% for systemic isotretinoin respectively for 2005 and 2006 (refer to table 4.5). For the systemic isotretinoin products, the trade name Roaccutane® was prescribed and claimed at the highest percentage (34.8%) in 2005 and Acnetane® (35.9%) in 2006 (refer to table 4.5). Generally there was no major difference in the number of claims between the different products of isotretinoin, but Acnetane® indicated the largest increase in the number of products claimed (20.5%). (Refer to section 4.5.2)

- *The seventh specific aim was to determine the cost and prevalence difference between the innovator and the generic isotretinoin products.*

The generic form of systemic isotretinoin products was claimed at a highest percentage although the innovator product of isotretinoin was still claimed at a higher ratio (innovator vs. generic ratio of isotretinoin products was 2:1) in relation to the total database (ratio of 3:1) (refer to section 4.4.1). A slight shift towards generic prescribing (12.6%) was observed over the two study years although a further 50% shift towards generic use in isotretinoin products could have led to an estimated cost saving of R400 000 per year in this section of the private health care sector of South Africa (refer to section 4.4.1).

- *The eighth specific aim was to identify the differences in prescribing patterns of isotretinoin between the major medical prescribers of isotretinoin.*

Dermatologists played the biggest role in prescribing isotretinoin in both study years (68.2% and 65.7% respectively for 2005 and 2006 (refer to table 4.8)) even though only 165 registered dermatologists practise in South Africa (Dermatology Society of South Africa, 2008). This percentage was, however, lower than statistics in the USA where 90% of isotretinoin prescriptions were prescribed by dermatologists and only 8% by general practitioners (Wysowski *et al.,* 2002:507). In comparison it was also identified that 27.5% and 29.7% of isotretinoin prescriptions were prescribed by general practitioners. (Refer to section 4.6.1)

Dermatologists indicated a higher average cost per isotretinoin prescription when compared to general practitioners (refer to table 4.8). This may be due to a higher percentage of innovator isotretinoin prescriptions prescribed by dermatologists, indicating that dermatologists may be more reluctant in prescribing the generic products of isotretinoin. (Refer to section 4.6.4)

- *The ninth specific aim was to identify age group differences in the prescribing patterns of isotretinoin.*

The number of isotretinoin prescriptions (n = 131) for patients under the age of 12 years is a concern, since the use of isotretinoin in this age group is not recommended (Leyton *et al.*, 2006:774). The teenage group (12 to 19 years) represented almost half of all isotretinoin prescriptions claimed in both study years and the combined age group including 19 to 27

years (12 to 27 years) represented more than 75% of prescriptions in both the study years (refer to section 4.7.1). This correlates with the high prevalence of acne in these age groups (Pal, 1997:4).

The teenage group also had the highest average cost per isotretinoin prescription and therefore presented the highest total cost for isotretinoin prescriptions. This indicated that isotretinoin had a high estimated cost of R275 000 and R260 000 per 10 000 beneficiaries in the teenage group, 12 to 19 years, respectively for 2005 and 2006. The age group above 35 years (which has a low acne prevalence) had the lowest average cost per isotretinoin prescription and indicated that isotretinoin cost only represented an estimated cost of R12 500 and R11 100 per 10 000 beneficiaries in this specific age group. (Refer to section 4.7.2)

More than 55% of patients claiming their isotretinoin prescriptions were past the teenage years (refer to section 4.7.5), indicating that a higher number of patients past these years were using isotretinoin compared to the US statistics (only 40%) (Fleisher *et al.,* 2003:665). This trend indicated that in relation to the US, South African patients using isotretinoin in this section of the private healthcare sector were of a higher age. (Refer to section 4.7.5)

- *The tenth specific aim was to determine and identify the difference in the prescribing patterns of isotretinoin in the different genders.*

Female patients received a higher number of isotretinoin prescriptions (56.2% and 57.4% respectively for 2005 and 2006 (refer to table 4.14)), although the teratogenicity effect only applies to the female gender. The ratio of female and male patients claiming isotretinoin treatment (almost at 60% female patients in relation to 40% male patients (refer to table 4.15)) in this study differed from the equally distributed use of isotretinoin between genders identified in the USA (Wysowski *et al.*, 2002:507; Asoulay *et al.*, 2006:670).

It was found that for both male and female patients more systemic isotretinoin items were claimed in relation to topical retiniods (refer to section 4.8.4) indicating that prescribers prefer systemic isotretinoin to topical retinoids even though the global alliance recommended that topical retinoids should be the primary treatment for all forms of acne and systemic isotretinoin should only be used in severe cases of acne (Gollnick et al., 2003:S9).

The median age of female patients using isotretinoin was 21 years and 18 years in male patients in both study years. A decrease in age was noted from a previous study done almost

a decade ago. Female patients received the highest number of isotretinoin prescriptions in all the age groups identified except in the teenage group where more isotretinoin prescriptions were claimed for male patients. (Refer to section 4.9)

However, the number of female patients claiming isotretinoin, especially female patients of child-bearing potential remains a concern (refer to section 4.9). Studies indicated that pregnancies did occur while female patients were using isotretinoin in spite of guidelines that were implemented to prevent these pregnancies (Bernard *et al.,* 2007:200, Garcia-Bournussen *et al.,* 2008:12). Further studies on the occurrence of pregnancies with concurrent use of isotretinoin in South Africa may be necessary. One has to identify the necessity to implement strict managing programmes (as seen in the USA) or the extension of regulatory programmes/guidelines in South Africa.

- *The eleventh specific aim was to identify combination therapy with isotretinoin products and determine any possible concerns.*

Isotretinoin was prescribed and claimed alone on a prescription in about 70% of prescriptions in both 2005 and 2006 (refer to section 4.10.1). Combined prescribing of medicine occurred at a higher percentage than in the USA (Wysowski *et al.*, 2002:507) where 91% of isotretinoin prescriptions were prescribed alone.

The most prevalent types of medicine identified on the same prescription as isotretinoin included oral contraceptives, antibiotics, corticosteroids, tear replacements and retinoids (refer to table A7.1 and A7.2 in appendix A).

Oral contraceptives were only prescribed in combination with isotretinion in 8.6% and 9.2% of prescriptions claimed for female patients (refer to section 4.10.2), indicating that it is important to do further studies on the adherence to isotretinoin guidelines in female patients, especially those of child-bearing potential.

Combinations of systemic isotretinion with systemic antibiotics (especially co-trimoxazole) presented with a lower average cost per prescription, indicating a lower dose of systemic isotretinoin prescribed (refer to section 4.10.3). Further studies on the clinical relevancy of systemic isotretinoin in combination with systemic antibiotics and the effect on cost are necessary.

Tear replacements were prescribed in combination with isotretinion to combat the side-effect of dry eyes/conjunctivitis. This occurred in 3.5% and 2.4% of isotretinoin prescriptions,

indicating extra costs involved with isotretinoin therapy, making this expensive drug even more expensive by treating the side-effects.

Systemic isotretinoin was also found to be combined with a topical retinoid, in 2.5% and 3.1% of prescriptions, but further studies need to be done to validate the necessity of such combined prescribing and usage.

The number of prescriptions containing systemic isotretinion combined with a systemic tetracycline is a concern, 139 and 130 prescriptions claimed were identified containing both of these products. Drug interactions identified could lead to benign intracranial hypertension (FDA, 2005; Gibbon *et al.*, 2005:194; Hanson & Leacman, 2001:177) and should be addressed as a concern.

5.2 RECOMMENDATIONS

Based only on the results of this study, the following recommendations can be made:

- The relatively high number of prescriptions containing the 20mg capsule of isotretinoin prescribed at an average of 53 capsules per prescription would seem to justify a recommendation that a 40mg capsule be introduced to the local market, as is available in the USA. This could be possible that by using a 40mg capsule rather than two 20mg capsules could be cost saving.

- It is recommended that generic use should be further promoted to reduce the costs of this relatively expensive acne treatment.

- Further studies to evaluate the possible misuse of systemic isotretinoin treatments for mild and moderate cases of acne in South Africa must be implemented.

- Studies, in the South African context, to investigate the prevalence of pregnancies while female patients are using isotretinoin are necessary in order to identify the necessity to incorporate strict prescribing programmes to prevent pregnancies from occurring.

- It is recommended that the prescribing patterns of systemic isotretinoin in combination with other antibiotics (especially co-trimoxazole) be investigated regarding the clinical as well as cost outcomes.

5.3 LIMITATIONS DURING THE STUDY

A number of limitations were encountered during the course of this research study. These limitations could possibly have had an effect on the results and conclusions obtained through this study. This should thus be taken into account when evaluating the results and conclusions. The following limitations were identified and experienced during this study:

- The database did not contain complete information on the diagnoses for the specific drug use due to incomplete ICD-10 codes. The primary indication of the specific drug was used to identify the use. This means, for example, that the oral contraceptives that were indicated for acne (e.g. Minerva®) could have been used only as an oral contraceptive and not for acne, but the drug was still classified under acne medicine.

- The clinical outcomes of the treatment could not be quantified. The occurrence of a second or third treatment course could also not be identified.

- The MIMS® classification system used to identify acne products did not include all types of antibiotics also used as acne treatment (e.g. co-trimoxazole). This meant that certain products that could also be used as acne treatment, but are excluded by the MIMS® classification system, were also excluded from the acne products identified.

- Concurrent use of other medicine or supplements with isotretinoin, which did not occur on the same claim, could not be identified. Thus interactions with other drugs and supplements used by the patient in combination with isotretinoin could not be identified.

- Certain patients were not classified in age groups nor gender as neither their age nor their gender were recorded in the data, and such unknown data were excluded from calculations.

- The amounts and the percentage that were calculated from the database were only valid for the medical aids that claimed through this database. Therefore this cannot be used as a true indication of isotretinoin prescribing patterns, nor will it reflect the true cost of dermatological usage in South Africa as a whole.

5.4 CHAPTER SUMMARY

The study was concluded in this chapter. All the objectives and research questions were addressed. Recommendations that were derived after completion of this study, as well as the limitations that were encountered during the course of the study, have been discussed. This chapter concludes this study.

APPENDIX A

Table A1.1: Frequency of the number of isotretinoin prescriptions claimed per patient for the years 2005 and 2006.

Year	Prescriptions per patient	Number of patients	Percentage (%)*
2005	**1**	2 508	39.0
	2	1 064	16.6
	3	757	11.8
	4	635	9.9
	5	572	8.9
	6	422	6.6
	7	239	3.7
	8	115	1.8
	9	52	0.81
	10	31	0.48
	11	16	0.25
	12	10	0.16
	13	3	0.05
	14	2	0.03
	16	1	0.02
	Total	**6 427**	**100**
2006	**1**	2 588	37.4
	2	1 134	16.4
	3	934	13.5
	4	725	10.5
	5	583	8.4
	6	484	7.0
	7	248	3.6
	8	104	1.5
	9	55	0.79
	10	32	0.46
	11	17	0.25
	12	17	0.25
	13	4	0.06
	15	2	0.03
	Total	**6 927**	**100**

*Percentage calculated according to the total number of patients for the specific year.

Table A1.2: The frequency of the top 5 claimed acne medicine according to total cost of the active ingredient for the years 2005 and 2006.

Year	Position	Active ingredient	Number of acne medicine items	Total cost	%*
2005	1	Isotretinoin	21 632	6 810 090	34.4
	2	Cyproterone/ ethinylestradiol	39 994	4 211 606	21.3
	3	Adapalene	10 837	1 918 790	9.7
	4	Benzoyl peroxide/ erythromycin	4 182	998 180	5.0
	5	Tretinoin	4 957	748 676	3.8
2006	1	Isotretinoin	23 532	6 533 241	36.3
	2	Cyproterone/ ethinylestradiol	38 798	3 727 359	20.7
	3	Adapalene	11 111	1 929 733	10.7
	4	Erythromycin/ zinc acetate	5 891	783 407	4.4
	5	Tretinoin	5 268	734 390	4.1

*Percentage was calculated according to total cost of acne medicine claimed in the specific year.

Table A2: Number of prescriptions per age group for the total database for 2005 and 2006.

Year	Age group	Number of prescriptions (n)	%*	Average number of prescriptions per patient	Total cost
2005	1	807 171	9.5	3.88 ± 3.79	114 560 977
	2	435 904	5.1	3.42 ± 3.53	72 238 615
	3	446 146	5.2	4.05 ± 4.47	76 687 367
	4	729 540	8.6	5.35 ± 5.97	124 460 176
	5	6 103 813	71.6	9.22 ± 9.13	1 505 428 532
	Total	**8 522 574**	**100**		**1 893 376 921**
2006	1	834 802	9.2	4.08 ± 3.95	119 842 186
	2	459 105	5.1	3.58 ± 3.68	76 857 542
	3	491 137	5.4	4.19 ± 4.66	83 509 162
	4	738 273	8.2	5.36 ± 6.12	125 214 611
	5	6 522 821	72.1	9.37 ± 9.36	1 641 519 393
	Total	**9 046 138**	**100**		**2 046 944 383**

*Percentage was calculated according to the total number of prescriptions on the database for the specific year.

Table A3: Frequency of acne medicine items claimed according to age groups for 2005 and 2006.

Year	Age group	Active ingredient and position	Frequency	Percentage (%)*
2005	**1**	1. Adapalene	201	15.9
		2. Methylprednisolone/neomycin	129	10.2
		3. Benzoyl Peroxide	120	9.5
		4. Tretinoin	114	9.0
		5. Isotretinoin	91	7.2
	2	1. Isotretinoin	10 591	23.6
		2. Cyproterone acetate/Ethinylestradiol	9 383	20.9
		3. Adapalene	5 582	12.4
		4. Erythromycin/Zinc acetate	2 631	5.9
		5. Benzoyl Peroxide	2 326	5.2
	3	1. Cyproterone acetate/Ethinylestradiol	18 550	49.1
		2. Isotretinoin	5 788	15.3
		3. Adapalene	2 535	6.7
		4. Benzoyl Peroxide	1 207	3.2
		5. Cyproterone	1 206	3.2
	4	1. Cyproterone acetate/Ethinylestradiol	6 580	42.2
		2. Isotretinoin	1 834	11.8
		3. Methylprednisolone/neomycin	1 141	7.3
		4. Adapalene	932	6.0
		5. Doxycycline	607	3.9
	5	1. Cyproterone acetate/Ethinylestradiol	5 441	19.4
		2. Isotretinoin	3 328	11.8
		3. Methylprednisolone/neomycin	2 805	10.0
		4. Doxycycline	2 682	9.5
		5. Tretinoin	2 665	9.5
2006	**1**	1. Adapalene	213	18.9
		2. Benzoyl Peroxide	108	9.6
		3. Erythromycin/Zinc acetate	105	9.3
		4. Tretinoin	101	9.0
		5. Doxycycline	84	7.5
		(Isotretinoin (7th))	(60)	(5.3)
	2	1. Isotretinoin	11 351	26.2
		2. Cyproterone acetate/Ethinylestradiol	8 530	19.6
		3. Adapalene	5 445	12.6
		4. Erythromycin/Zinc acetate	2 929	6.8

		5. Minocycline	2 335	5.4
	3	1. Cyproterone acetate/Ethinylestradiol	18 586	49.2
		2. Isotretinoin	6 604	17.5
		3. Adapalene	2 757	7.3
		4. Erythromycin/Zinc acetate	1 229	3.4
		5. Benzoyl Peroxide	1 228	3.3
	4	1. Cyproterone acetate/Ethinylestradiol	6 222	42.3
		2. Isotretinoin	2 027	13.8
		3. Adapalene	917	6.2
		4. Doxycycline	624	4.2
		5. Methylprednisolone/neomycin	607	4.1
	5	1. Cyproterone acetate/Ethinylestradiol	5 408	20.0
		2. Isotretinoin	3 490	12.9
		3. Tretinoin	2 774	10.3
		4. Doxycycline	2 493	9.2
		5. Adapalene	1 779	6.6

*Percentage was calculated according to the total number of acne medicine items claimed for the specific year.

Table A4: The prevalence and average cost according to gender per prescription of the total database for 2005 and 2006.

Year	Gender	Number of prescriptions	%	Average cost (R)	Total cost (R)
2005	Female	5 112 269	59.99	220.77 ± 455.62	1 128 652 112
	Male	3 403 117	39.93	224.27 ± 473.73	763 226 111
	Unspecified	7 192	0.08	208.38 ± 643.60	1 498 697
2006	Female	5 421 011	59.92	223.77 ± 532.49	1 213 068 356
	Male	3 620 958	40.02	229.97 ± 592.88	832 725 542
	Unspecified	4 875	0.05	236.00 ± 536.55	1 150 484

*Percentage was calculated according to the total number of prescriptions claimed in the specific year

Table A5: Number of patients according to gender on the total database for 2005 and 2006.

Year	Gender	Number of patients	%*
2005	Female	675 814	55.5
	Male	540 874	44.4
	Unspecified	1 670	0.14
2006	Female	698 477	55.5
	Male	559 535	44.4
	Unspecified	1 087	0.09

*Percentage calculated according to total number of patients for the specific year.

Table A6: The frequency of the claimed active ingredients for acne medication per gender for 2005 and 2006.

Year	Gender	Ingredient	Frequency (n)	Percent (%)*	Cumulative percent (%)
2005	**Female**	Cyproterone acetate/Ethinylestradiol	39 862	42.0	42.0
		Isotretinoin	12 081	12.7	54.8
		Adapalene	6 953	7.3	62.1
		Methylprednisolone/neomycin	4 706	5.0	67.0
		Tretinoin	3 831	4.0	71.1
		Erythromycin/zinc acetate	3 179	3.4	74.4
		Bensoyl peroxide	3 112	3.3	77.7
		Minocycline	3 075	3.2	81.0
		Doxycycline	3 000	3.2	84.1
	Male	Isotretinoin	9 543	29.2	29.2
		Adapalene	3 865	11.9	41.0
		Methylprednisolone/neomycin	2 463	7.5	48.5
		Minocycline	2 284	7.0	55.5
		Doxycycline	2 271	6.9	62.4
		Bensoyl peroxide	2 199	6.7	69.2
		Erythromycin/zinc acetate	1 927	5.9	75.0
		Bensoyl peroxide/erhythromycin	1 712	5.2	80.3
		Azeliac acid	1 131	3.5	83.7
		Tretinoin	1 121	3.4	87.2
		Miconazole/Benzoyl peroxide	1 120	3.4	90.6
2006	**Female**	Cyproterone acetate/Ethinylestradiol	38 681	41.7	41.7
		Isotretinoin	13 457	14.5	56.3
		Adapalene	7 076	7.6	63.9
		Tretinoin	4 062	4.4	68.3
		Erythromycin/zinc acetate	3 751	4.1	72.3
		Bensoyl peroxide	3 230	3.5	75.8
		Minocycline	3 129	3.4	79.2
		Doxycycline	3 108	3.4	82.5
		Methylprednisolone/neomycin	2 895	3.1	85.7
	Male	Isotretinoin	10 062	32.2	32.2
		Adapalene	4 022	12.9	45.1
		Minocycline	2 179	7.0	52.1
		Doxycycline	2 160	6.9	59.0
		Erythromycin/zinc acetate	2 122	6.8	65.8
		Bensoyl peroxide	2 082	6.7	72.4
		Methylprednisolone/neomycin	1 484	4.8	77.2
		Tretinoin	1 203	3.9	81.1
		Azeliac acid	1 117	3.6	84.6

*Active ingredient for acne medication with a prevalence of less than 3.0 % was excluded from the table.

Table A7.1: The products prescribed in combination with isotretinoin for the year 2005.

Pos	Isotretinoin medicine item 1 (®)	Isotretinoin medicine item 2 (®)	Combined medicine item (®)	Frequency	%*	Average cost per combination prescription (R)	Standard deviation	Total cost of combination (R)
1	ROACCUTANE 20MG			3 479	18.7	493.42	229.65	1 716 595
2	ACNETANE 20MG			3 192	17.2	355.77	152.83	1 135 607
3	ORATANE 20MG			2 773	14.9	360.59	157.76	999 906
4	ROACCUTANE 10MG	ROACCUTANE 20MG		773	4.2	615.98	211.77	476 150
5	ORATANE 10MG			614	3.3	121.64	67.05	74 689
6	ACNETANE 10MG	ACNETANE 20MG		610	3.3	418.63	145.41	255 364
7	ORATANE 10MG	ORATANE 20MG		607	3.3	421.52	134.47	255 865
8	ACNETANE 10MG			605	3.3	124.07	62.10	75 062
9	ROACCUTANE 10MG			513	2.8	187.21	100.72	96 038
10	ISOTREX GEL			159	0.86	98.94	21.72	15 732
11	ROACCUTANE 20MG		MINERVA	64	0.35	514.57	223.65	32 933
12	ROACCUTANE 20MG		PURBAC TAB	61	0.33	216.35	183.69	13 198
13	ACNETANE 20MG		MINERVA	59	0.32	427.37	157.13	25 215
14	ORATANE 20MG		MINERVA	52	0.28	413.05	169.23	21 478
15	ACNETANE 20MG		TEARS NATURALE II DROPS	37	0.20	572.90	136.47	21 197
16	ORATANE 10MG	ORATANE 20MG	TEARS NATURALE II DROPS	34	0.18	515.12	100.52	17 514
17	ORATANE 20MG		TEARS NATURALE II DROPS	33	0.18	568.97	140.51	18 776
18	ROACCUTANE 20MG		DIANE-35	32	0.17	524.95	207.99	16 798
19	ACNETANE 20MG		TEARGEL 10ML 2MG/GM	31	0.17	429.67	67.40	13 320
20	ISOTREX GEL		TETRALYSAL 300MG CAP	30	0.16	306.90	42.36	9 207
21	ROACCUTANE 20MG		DIFFERIN CREAM	30	0.16	483.18	262.24	14 496
22	ORATANE 20MG		ADCO-ERYTHROMYCIN 250	29	0.16	273.93	38.61	7 944
23	ACNETANE 20MG		YASMIN	28	0.15	375.99	176.81	10 528
24	ROACCUTANE 20MG		YASMIN	28	0.15	522.49	201.33	14 630
25	ROACCUTANE 20MG		TEARGEL 10ML 2MG/GM	26	0.14	606.71	158.52	15 774
26	ORATANE 20MG		PURBAC TAB	25	0.13	309.74	186.52	7 744
27	ROACCUTANE 20MG		TEARS NATURALE II DROPS	25	0.13	612.88	172.01	15 322

28	ACNETANE 10MG	ACNETANE 20MG	TEARS NATURALE II DROPS	24	0.13	608.29	187.33	14 599
29	ACNETANE 20MG		GINETTE	23	0.12	413.37	218.67	9 508
30	ORATANE 20MG		FUCIDIN CREAM	21	0.11	424.20	88.80	8 908
31	ORATANE 20MG		GINETTE	21	0.11	434.72	140.37	9 129
32	ISOTREX GEL		CYCLIMYCIN 50MG CAP	20	0.11	232.54	51.63	4 651
33	ORATANE 10MG		MINERVA	20	0.11	243.40	104.29	4 868
34	ORATANE 10MG	ORATANE 20MG	PURBAC TAB	20	0.11	294.38	179.66	5 888
35	ACNETANE 20MG		DIFFERIN GEL	19	0.10	566.20	172.09	10 758
36	ORATANE 20MG		BE-TABS PREDNISONE 5MG	19	0.10	488.95	146.56	9 290
37	ROACCUTANE 20MG		DIFFERIN GEL	19	0.10	529.46	212.67	10 060
38	ROACCUTANE 20MG		REFRESH 0.4ML SOL	19	0.10	655.10	115.92	12 447
	TOTAL			**14 174****	**76.2**			

*Percentage calculated according to total number of isotretinoin prescriptions claimed.

**The total number of prescriptions listed in this table.

Legend: CAP = capsule

TAB = tablet

SOL = solution

Table A7.2: The products prescribed in combination with isotretinoin for the year 2006.

Pos	Isotretinoin medicine item 1 (®)	Isotretinoin medicine item 2 (®)	Combined medicine item (®)	Frequency	%*	Average cost per combination prescription (R)	Standard deviation	Total cost of combination (R)
1	ACNETANE 20			3 794	18.8	314.98	142.64	1 195 046
2	ORATANE 20MG			3 108	15.4	316.12	143.61	982 502
3	ROACCUTANE 20MG			3 087	15.3	459.39	234.97	1 418 128
4	ACNETANE 10	ACNETANE 20		760	3.8	353.68	150.52	268 798
5	ROACCUTANE 10MG	ROACCUTANE 20MG		742	3.7	557.95	235.99	414 000
6	ACNETANE 10			720	3.6	114.36	55.76	82 341
7	ORATANE 10MG	ORATANE 20MG		686	3.4	389.80	152.97	267 405
8	ORATANE 10MG			609	3.0	113.60	63.63	69 184
9	ROACCUTANE 10MG			507	2.5	177.29	91.93	89 885
10	ISOTREX GEL			161	0.80	91.58	26.82	14 744
11	ROACCUTANE 20MG		MINERVA	86	0.43	401.08	249.29	34 493
12	ORATANE 20MG		MINERVA	80	0.40	382.85	174.72	30 628
13	ACNETANE 20		MINERVA	51	0.25	397.29	164.40	20 262
14	ISOTREX GEL		TETRALYSAL 300MG CAP	48	0.24	289.00	76.28	13 872
15	ORATANE 20MG		BE-TABS PREDNISONE 5MG	48	0.24	437.11	193.12	20 981
16	ORATANE 20MG		YASMIN TAB	46	0.23	392.47	149.72	18 054
17	ACNETANE 20		PURBAC TAB	44	0.22	185.58	172.60	8 166
18	ROACCUTANE 20MG		PURBAC TAB	39	0.19	266.74	310.57	10 403
19	ROACCUTANE 20MG		BE-TABS PREDNISONE 5MG	37	0.18	580.20	209.84	21 467
20	ACNETANE 20		TEARS NATURALE II DROPS	34	0.17	465.62	108.11	15 831
21	ACNETANE 20		YASMIN TAB	33	0.16	490.32	103.99	16 181
22	ACNETANE 20		TEARGEL 10ML 2MG/GM	32	0.16	439.64	65.53	14 069
23	ROACCUTANE 20MG		TEARS NATURALE II DROPS	31	0.15	504.68	197.59	15 645
24	ACNETANE 20		GINETTE	29	0.14	409.73	148.67	11 882
25	ACNETANE 10		DIFFERIN CREAM	28	0.14	248.41	42.03	6 956
26	ROACCUTANE 20MG		DIFFERIN CREAM	28	0.14	478.52	290.15	13 398
27	ACNETANE 10		BENZAC AC 5 GEL	27	0.13	176.77	46.95	4 773

28	ROACCUTANE 20MG		DIANE-35 TAB	27	0.13	613.73	227.06	16 571
29	ACNETANE 20		DIFFERIN CREAM	26	0.13	371.69	136.19	9 664
30	ORATANE 10MG	ORATANE 20MG	PURBAC TAB	26	0.13	343.92	179.37	8 942
31	ORATANE 20MG		ZINERYT TOPICAL ACNE LOT	26	0.13	380.89	138.87	9 903
32	ACNETANE 10	ACNETANE 20	TEARS NATURALE II DROPS	25	0.12	409.88	251.66	10 247
33	ISOTREX GEL		PURBAC TAB	25	0.12	124.17	30.09	3 104
34	ORATANE 20MG		TEARS NATURALE II DROPS	25	0.12	483.91	151.80	12 098
35	ACNETANE 10	ACNETANE 20	TEARGEL 10ML 2MG/GM	24	0.12	470.11	66.77	11 283
36	ROACCUTANE 20MG		DIFFERIN CREAM	23	0.11	297.10	20.97	6 833
37	ACNETANE 20		MYLOCORT 1GM/100GM CR	22	0.11	322.47	162.06	7 094
38	ORATANE 20MG		PANAFCORT 5MG TAB	22	0.11	307.24	107.86	6 759
39	ACNETANE 20		ILOTYCIN-A CREAM	21	0.10	329.13	140.04	6 912
40	ISOTREX GEL		ZINERYT TOPICAL ACNE LOT	21	0.10	227.71	11.92	4 782
41	ACNETANE 10		MINERVA	20	0.10	177.93	39.94	3 559
42	ACNETANE 10	ACNETANE 20	DIFFERIN CREAM	20	0.10	412.30	183.05	8 246
43	ORATANE 20MG		PURBAC TAB	20	0.10	323.53	143.87	6 471
	TOTAL			**15 268****	**75.5**			

* Percentage calculated according to total number of isotretinoin prescriptions claimed.

**The total of prescriptions listed in this table.

Legend: CAP = capsule

TAB = tablet

LOT = lotion

CR = cream

Only the frequency of the combinations occurring more than 0.1% of the total number of prescriptions was listed in Table A7.1 and Table A7.2.

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