

**THE IMPACT OF THE INTRODUCTION OF AN ENANTIOMER OF AN
ALREADY MARKETING RACEMIC PHARMACEUTICAL PRODUCT
ON DRUG UTILIZATION AND MARKET SHARE IN THE SOUTH
AFRICAN PHARMACEUTICAL MARKET.**

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DEDICATION

This research report is dedicated to my parents, Raj and Karuna Mestry. Their passion for life-long learning has inspired me and I endeavour to emulate their determination and perseverance to achieve success in all facets of life.

DECLARATION

I, Saiyuri Nair, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Pharmaceutical Affairs at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other university.

Signature

Date: February 2014

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This research report would not have been possible without my academic supervisors Mrs Shirra Moch and Dr. Jacqui Miot. Despite their busy schedules, they were always readily available and I am grateful for all the advice, guidance and support given to me throughout this undertaking.

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IV. ABBREVIATIONS

AUC	Area Under Curve
API	Active Pharmaceutical Ingredient
Cmax	Maximum concentration
CPI	Consumer Price Index
CYP	Cytochrome P
EDL	Essential Drugs List
F.C	Film Coated
FDA	Federal Drug Administration
MADRS	Montgomery Asberg depression rating scale
MAT	Moving Annual Total
MCC	Medicines Control Council
OTC	Over the counter
PPI	Proton Pump Inhibitor
R&D	Research and Development
RCTs	Randomized Controlled Trials
SE	Single Enantiomer
SEP	Single Exit Price
SERT	Serotonin Reuptake Transporter
SSRI	Selective Serotonin Reuptake Inhibitor
TPM	Total Private Market
TRIPS	Trade Related Aspects of Intellectual Property Rights

V. ABSTRACT

BACKGROUND:

Stereochemistry is often used in the development of drugs. Enantiomers of a chiral drug are two non-superimposable mirror images of the molecule and a racemic mixture consists of equal quantities of both enantiomers. This study looks at the phenomenon of “chiral switching” where a molecule previously developed and marketed by an innovator company as a racemate medicine is later developed and launched as a single enantiomer. Drug utilization and market share data of three molecules that underwent chiral switching were investigated retrospectively to determine the clinical and economic impact of these occurrences in the private South African pharmaceutical market.

METHOD:

Unit sales and rand sales data of the racemate (and its generics) and the single enantiomer of three drug substance pairs, namely omeprazole-esomeprazole, citalopram-escitalopram and cetirizine-levocetirizine were gathered a year preceding the launch of the single enantiomer to three years subsequent to the launch of the single enantiomer onto the private market.

DATA ANALYSIS:

Descriptive statistical analysis included plotting trend lines of the annual unit and rand sales of both the racemate (and its generics) and the single enantiomer products during the study period, pie charts illustrating the year on year differences in market share (in both unit sales and rand value of sales) as well as box and whisker plots of the racemate and its generics plotted for the year before the single enantiomer was launched, the year after its launch, two years after launch and three years after launch.

The probability of the enantiomer being prescribed/ sold instead of the racemate at different time points was also calculated to determine whether the drug utilization of the single enantiomer increased or decreased from introduction until three years subsequent to its launch.

CONCLUSION:

Results were consistent with global literature indicating that “chiral switching’ is a successful strategy employed by innovator companies to extend their market share. Drug utilization of the single enantiomer generally showed an upward trend following its launch indicating that there is a perceived belief of enhanced clinical outcomes for the patient. There are, however, many other influencing factors such as pricing strategies, prescription status, marketing efforts to physicians and/or consumers and patent challenges specific to each market that make it difficult to draw a general conclusion from the case studies.

1. INTRODUCTION

Chirality is defined by McConathy and Owens (2003) as the geometric characteristic of a drug or molecule of not being superimposable on its mirror image. The two mirror images of the chiral molecule are known as enantiomers. A racemate consists of equal quantities of both enantiomers of the chiral drug.

Chirality is an important consideration in the pharmaceutical industry as it has implications on the pharmacology of drug molecules by introducing selectivity and often specificity of drug action (Tucker, 2000).

The thalidomide tragedy that occurred in the 1950's is a well-known example that highlights the importance of chirality in medicines. Thalidomide was considered to be a fairly safe sedative, but foetal abnormalities saw it being withdrawn from the market. Investigative studies yielded interesting results: only the (S)-enantiomer was responsible for the teratogenic effects. Sedative effects were dependent on concentrations of the (R)-enantiomer.

It was believed the disaster could have been averted had the pure (R)-enantiomer been administered instead of the racemate, however research has since showed that there is rapid interconversion of the thalidomide enantiomers in vivo making enantioselectivity nearly impossible (Waldeck, 2003).

Perhexiline is another compound that illustrates how different enantiomers of the same compound can influence the safety and efficacy of a medicine. Perhexiline was an anti-angina medicine introduced by Richardson–Merrell Pharmaceuticals in the late 1960s into the French market followed by other countries including the United Kingdom, Australia and New Zealand. Although effective in treating angina, severe cases of hepatotoxicity and neurotoxicity were reported from the use of perhexiline and it was subsequently withdrawn from many markets by the late 1980's. It continues to be used in Australia and New Zealand under strict patient care (Ashrafian *et al*, 2007). Pharmacokinetic studies undertaken by Gould *et al* (1986) into perhexiline which consists of a racemic mixture of (+) and (-) enantiomers revealed that the (-)-perhexiline was metabolized more slowly than (+)-perhexiline by the CYP enzymes in the liver thereby causing hepatotoxicity.

Most regulatory authorities are cognisant of the significance of enantiomers when developing medicines, South Africa being no different. The regulatory Biostudies

guidelines (Medicines Control Council, 2011) issued by the South African health authority, the Medicines Control Council (MCC), addresses the issue of the registration of enantiomers and racemates by recommending the following:

- (1) measurement of the individual enantiomers for bioavailability studies
- (2) measurement of the racemate using an achiral assay for bioequivalence testing
- (3) measurement of individual enantiomers only if:
 - different pharmacodynamics characteristics are demonstrated by the enantiomers
 - different pharmacokinetic characteristics are demonstrated by the enantiomers
 - the minor enantiomer is responsible for the primary safety and efficacy properties
 - non-linear absorption occurs for at least one of the enantiomers (change in concentration of enantiomer ratio according to input rate of drug or Active Pharmaceutical Ingredient (API)).

The introduction of a single enantiomer based pharmaceutical medicine of an already marketed racemic mixture is known as “chiral switching” (Hutt and Valentova, 2003).

Clinical and pharmacological comparisons between the single enantiomer drug product and its racemic mixture (and/ or similar medicines in its drug class) are commonly found in the literature. Authors such as Birkett (1989) and Ariën (1984) are wholly in favour of single enantiomer drugs over racemates. Birkett (1989) states that “balance will gradually change to a situation where enantiomerically pure drugs will be the standard”. Other authors such as Hutt and Valentova (2003) and Tucker (2000), give a more balanced view on the topic, citing not only examples of successful cases where there were clinical and safety advantages of single enantiomers over their racemates but also examples of single enantiomers that failed to provide an advantage over their racemate. In contrast, Mansfield *et al* (2004) is not in favour of single enantiomers, seeing no significant clinical advantage over the racemic drugs.

A drug utilization review can be used to ascertain whether the possible increase in efficacy and patient safety of the single enantiomer drug product has an impact on prescribing/usage trends.

Besides the positive clinical perspective on this subject, chiral switching is also used as a strategy employed by innovator pharmaceutical companies to prolong the economic life-cycle of a particular molecule.

This study combines drug utilization reviews and market share information to determine the impact of the introduction of an enantiomer of an already marketed racemic pharmaceutical product in a South African context.

Three diverse racemate-enantiomer drug pairs were analysed:

- (1) omeprazole and esomeprazole – a prescription only gastro-intestinal medicine
- (2) citalopram and escitalopram – a prescription only medicine prescribed for depressive disorders
- (3) cetirizine and levocetirizine – an anti-allergic medicine that is available without prescription or OTC (over-the-counter).

The importance of conducting such a study was to ascertain whether the single enantiomer of the racemate was perceived as more clinically beneficial as extrapolated from its utilization in practice as opposed to the original racemic mixture. Additionally, the investigation of the economic impact of the introduction of the single enantiomer on the innovator pharmaceutical company and its competitors adds to local knowledge on drug costing, consequent usage and impact on health care.

2. DEFINITIONS

Stereoisomers

Stereoisomers refer to molecules that are identical with regards to the chemical bonds the atoms share, but differ in how they are arranged spatially. (Brown *et al*, 2003)

Enantiomers

Enantiomers, also known as optical isomers, are molecules that are non-superimposable mirror images of each other. A molecule that cannot be superimposed on its mirror image is said to be chiral. Each enantiomer is optically active - if one rotates polarized light (light waves vibrating in a single plane) clockwise (R), the other enantiomer will rotate polarized light in a counter clockwise (S) direction (Brown *et al*, 2003).

Racemate

A mixture containing equivalent amounts of the two enantiomers is called a racemate and is optically inactive (Brown *et al*, 2003).

Market share:

Market share is defined by Howie and Kleczyk (2008) as the prescribing volume of a particular product group or brand expressed as a percentage of a defined total market.

Patent

A patent is a property right granted by an independent state to the inventor of an invention that is novel (not disclosed previously anywhere in the world), nonobvious (not obvious to a person ordinarily skilled in the field involved) and useful (Lehman, 2003).

Drug Utilisation Review (DUR)

The WHO defines drug utilisation as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” (WHO, 2003).

A retrospective DUR uses data that is collected and analysed after the prescription, dispensing, and use of medicines has occurred. These studies serve to identify trends in prescribing practices (Truter, 2008).

Innovator

An innovator product is the original drug product that has been developed by a pharmaceutical company. The innovator company is a holder of a patent preventing its molecule / formulation/ manufacture to be marketed by another company for a certain period of time.

Generic

A generic medicine or an interchangeable multisource medicine is defined by the Medicines and Related Substance Act 101 of 1965 (as amended) as containing “the same active substances which are identical in strength or concentration, dosage form and route of administration and meet the same or comparable standards, which comply with the requirements for therapeutic equivalence as prescribed”.

Single Exit Price (SEP)

All pharmaceutical companies in South Africa are mandated to sell their products at one set price to all customers.

This transparent pricing system was introduced by means of Government Gazette in November 2005 which provides the following definition of the single exit price: “The price set by the manufacturer or importer of a medicine or Scheduled substance in terms of these regulations combined with the logistics fee and VAT and is the price of the lowest unit of the medicine or Scheduled substance within a pack multiplied by the number of units in the pack.” (Department of Health, 2005)

3. BACKGROUND

3.1 Clinical Pharmacology of Racemates and Enantiomers.

Stereochemistry is an essential aspect to consider when developing drugs. The interaction that occurs between a drug and a biological system is initially stereospecific - beginning a sequence of events that ultimately leads to a certain measurable physiological response (Burke and Henderson, 2002).

The stereospecificity of biological receptors means that each enantiomer of a chiral drug may interact with the binding site in its own unique manner. This can lead to differences that can have either beneficial or detrimental consequences to the pharmacodynamics and pharmacokinetic properties of the drug.

These differences are illustrated in *Figure 1* below. The active enantiomer is spatially arranged so that part *A* of the molecule aligns with site *a* of the drug receptor, part *B* with site *b* and part *C* with site *c* and is therefore pharmacologically active. The simultaneous alignment of all parts of the molecule with their corresponding binding site is not achieved in the inactive enantiomer – preventing a biological effect (McConathy and Owens, 2003).

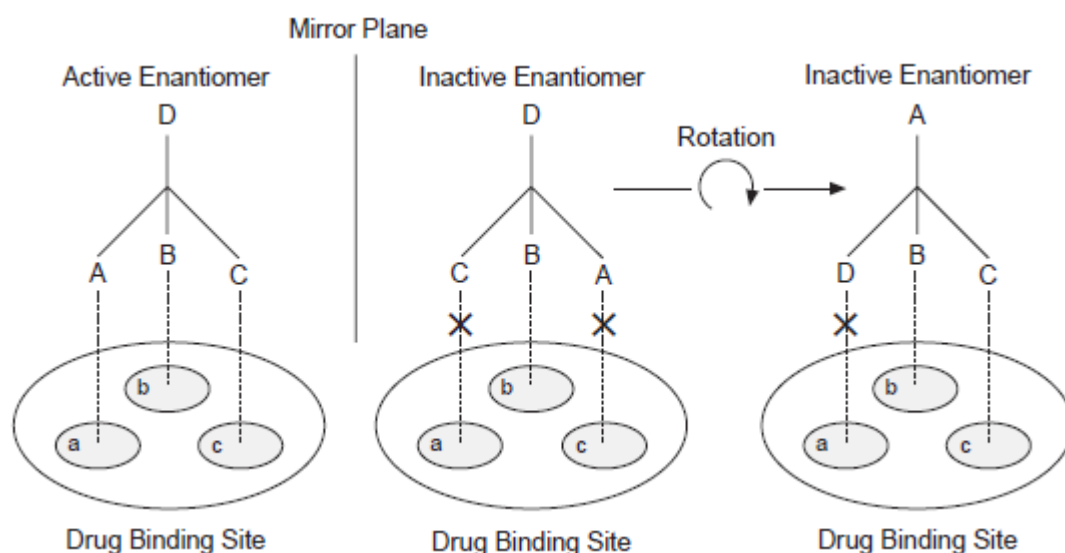


Figure 1: Interactional differences between two hypothetical enantiomers and their drug binding sites (McConathy and Owens, 2003)

However, as Caldwell (1992) points out, there are instances where the chiral centre is relatively uninvolved with the interaction occurring at the binding site and therefore the drug receptor does not differentiate between two enantiomers of the chiral drug.

According to Agranat and Caner (1999), there are four possible reasons why pure enantiomers are more beneficial than racemates:

- (1) a total dosage reduction could be achieved using a single enantiomer as opposed the racemate,
- (2) a less complex dose-response relationship can be accomplished,
- (3) patient variability with regard to pharmacokinetic and pharmacodynamics properties could be decreased,
- (4) reduction in toxicity of the inactive enantiomer is possible.

Caldwell (1992) advises that the decision of whether an enantiomer pure drug versus its racemate would be more beneficial must be made on a case by case basis.

Criteria to consider include:

- (1) The pharmacological and therapeutic advantage the enantiomer would provide. Studies should be conducted to measure the activity of each enantiomer at the binding site. The metabolic and pharmacokinetic profiles should be fully characterized as this could have implications for toxicity.
- (2) Ease of technically synthesizing enantiomer pure drug and how economical it would be. The methods and techniques to isolate enantiomers vary for each drug and can include chromatography, electrophoresis and crystallization. Most methods are intrinsically expensive, consume high amounts of organic solvents and can be time-consuming. Costs of equipment, materials, recycling and manpower as well as the environmental impact need to be taken into consideration (Carvalho *et al*, 2006).
- (3) Difficulty in extrapolating animal data to humans. This can be attributed to a multitude of differences in the genetic make-up of humans, high selectivity when choosing the test experimental population and laboratory test situations that do not reflect man and his environment adequately.
- (4) Possible marketing opportunities. This could include marketing an enantiomer pure drug as having a safer, more tolerable profile or enhanced activity.

A short introduction to the racemate-enantiomer drug molecules that will be analysed in this study follows:

3.1.1 Omeprazole to Esomeprazole

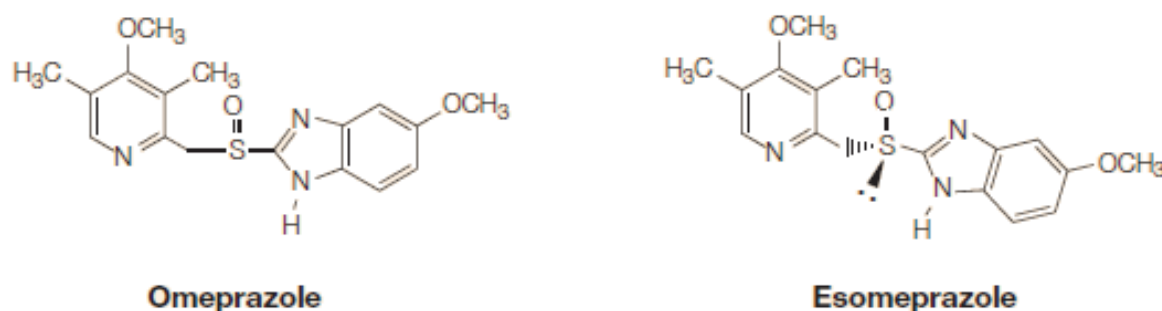


Figure 2: Stereochemistry of Omeprazole and Esomeprazole (Olbe *et al*, 2003).

Possibly the most successful chiral switch to take place was derived from omeprazole, manufactured by the Swedish pharmaceutical company Astra AB (now known as AstraZeneca following a merger with UK company Zeneca in 1999) and launched in South Africa in 1990.

Omeprazole is a Proton Pump Inhibitor (PPI) that effectively inhibits the secretion of acid from the parietal cells in the stomach. Omeprazole is a racemate consisting of both R- and S- enantiomers. Esomeprazole – the S enantiomer – was found to be superior due to its pharmacokinetic properties (Olbe *et al*, 2003) and launched in 2001 into the South African market by AstraZeneca Pharmaceuticals (Pty) Ltd. Both isomers are, however, equally effective in inhibiting acid secretion at the parietal-cell level as they are both converted to an identical achiral sulphonamide which inhibits the H^+K^+ ATPase proton pump (Kendall, 2003).

Pharmacokinetic studies conducted on esomeprazole by Andersson *et al* (2001) show that esomeprazole is metabolized more slowly than the (R)-isomer resulting in a less variable, higher bioavailability of esomeprazole when compared to the same dose of omeprazole. There was also less inter-individual variability in the AUC when using esomeprazole as compared to omeprazole.

Richter *et al* (2001) conducted a randomized, double-blind, 8 week study in 2 425 patients with erosive oesophagitis to compare esomeprazole to omeprazole. The results showed that esomeprazole had greater efficacy than omeprazole in treating

GERD (Gastro Esophageal Reflux Disease) – 93.7 % of patients were healed with esomeprazole by week 8 as opposed to 84.2 % of patients on omeprazole therapy ($p < 0.001$).

A randomized, crossover study done by Röhss *et al* (2002) comparing 40 mg of esomeprazole compared to 40 mg of omeprazole (twice the standard dose) also demonstrated esomeprazole has superior acid suppressant effect in patients with GERD.

3.1.2 Citalopram to Escitalopram

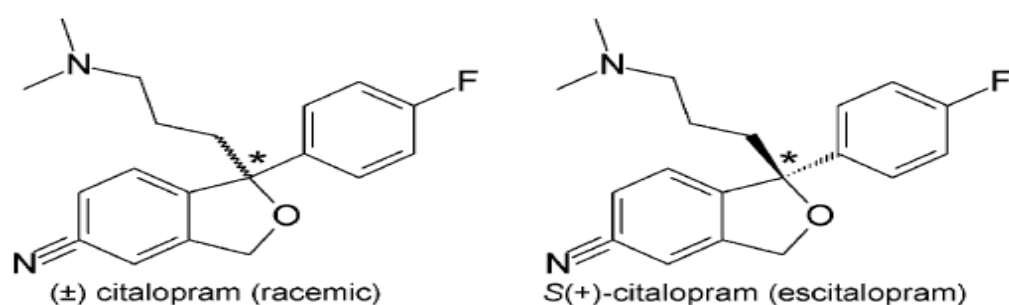


Figure 3: Stereochemistry of Citalopram and Escitalopram (Smith, 2009)

Citalopram is a selective serotonin re-uptake inhibitor (SSRI) used for the treatment of depression and anxiety disorders. It is the original racemic mixture manufactured and marketed by Lundbeck Pharmaceuticals as CIPRAMIL[®] since 2001.

Escitalopram (CIPRALEX[®]) was later launched in 2004 by Lundbeck Pharmaceuticals, the same innovator company of the original racemate CIPRAMIL[®]. Escitalopram is the active S-enantiomer of the racemate, citalopram, and demonstrates superior selective serotonin reuptake inhibition (Baumann *et al*, 2001).

A possible basis for this superior activity of escitalopram has been suggested by Sanchez *et al* (2004), who, after reviewing pharmacological and non-clinical literature, concluded that the R-enantiomer in the citalopram antagonistically occupies the binding site located on the serotonin transporter protein. The enhanced clinical effect that is observed could be the result of the removal of this inhibition.

Other reasons that favour escitalopram when compared to citalopram have been summarised by Leonard and Taylor (2010) as follows:

- Escitalopram allosterically modulates the serotonin reuptake transporter (SERT) leading to superior pharmacological potency.
- Metabolism of the R-enantiomer in citalopram occurs more gradually in comparison to the S-enantiomer. This leads to almost double the plasma concentration of the (R)-enantiomer, the accumulation of which is undesirable.
- Functional antagonism of the (R)-enantiomer on escitalopram occurs. The higher occupancy of the (R)-enantiomer at target sites prevents escitalopram from binding and leads to a reduction in activity.
- A quicker onset of action of escitalopram is possible as there is a faster desensitization of autoreceptors resulting in an augmented serotonin release. A rapid onset of action is clinically beneficial as there will be faster symptom control.

A meta-analysis of seven comparative randomized controlled trials (RCTs) that directly compared escitalopram and citalopram in depression was conducted by Trkulja (2010). The RCTs (all double blind, parallel grouped) involved out-patients that were mainly younger, healthy adults free of any other psychopathology and were conducted at multiple centres in different locations. Montgomery-Asberg depression rating scale (MADRS) scores at different evaluation time-points were compared. The author concluded that there was little evidence of significant clinical advantage of escitalopram versus citalopram on an equimolar basis for the short to medium term treatment of major depression.

The subject of intensive debate is whether *any* anti-depressant drug is superior to the placebo effect. Kirsch and Sapirstein (1998) conducted a meta-analysis on published literature and concluded that the effect of the placebo accounted for twice as much as the drug effect. Kirsch *et al* (2008) conducted a similar meta-analysis using clinical trial data submitted to the FDA on four new generation anti-depressants in order to eliminate any publication bias. They found minor statistically significant superiority of anti-depressants over the placebo but maintained that due to the small effect size this result was still clinically insignificant (Kirsch, 2008).

3.1.3 Cetirizine to Levocetirizine

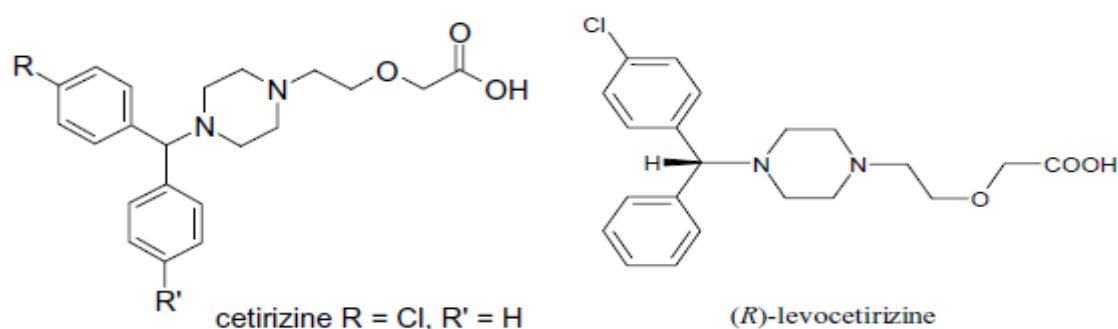


Figure 4: Stereochemistry of Cetirizine (Lewis *et al*, 2004) and Levocetirizine (Tillemant *et al*, 2003)

Cetirizine is an antihistamine, a potent H₁-receptor antagonist, used for the treatment of allergic rhinitis as well as urticarial conditions. It was launched by the Belgian Pharmaceutical company, UCB Pharma, as ZYRTEC[®] in 1994. Cetirizine is the racemic mixture of (R)-levocetirizine and (S)-dextrocetirizine.

Levocetirizine, the pharmacologically active R-enantiomer, was later registered and marketed by GlaxoSmithKline (Pty) Ltd (GSK) as XYZAL[®].

Pharmacological characteristics of the racemate, cetirizine, were compared to levocetirizine by Telliment *et al* (2003) and are discussed below:

- Levocetirizine demonstrates an increased affinity to the H₁ receptor and is considered to be the more pharmacologically active enantiomer (also known as the eutomer) compared to dextrocetirizine.
- Slightly higher plasma protein binding of levocetirizine could be responsible for the observed low volume distribution in the body as opposed to dextrocetirizine. This low volume of distribution decrease the amount of drug that is exposed to organs where toxic effects may be elicited, making levocetirizine more beneficial in terms of safety and efficacy, reducing the risk of dose-dependent toxicity and interindividual variation of therapeutic effect.
- The low volume of distribution also decreases the risk of possible drug-drug interactions (Telliment *et al*, 2003).

A study conducted by Baltes *et al* (2001) showed that the pharmacokinetic properties of levocetirizine were superior compared to dextrocetirizine due to higher plasma AUC (this reflects the actual exposure of the body to the drug after administration of the drug) and $C_{\max}$ (the maximum concentration the drug achieves in the test area after the first dose). Levocetirizine also demonstrated a longer half-life (time required for the drug to fall to half the value it was at the beginning of the time period) and lower volume of distribution (the distribution of drug between the plasma and the rest of the body tissue) in comparison to dextrocetirizine. A significantly lower non-renal clearance of levocetirizine was also observed which could result in decreased metabolism based drug interactions.

3.2 The Pharmaceutical Industry and Patents

According to the Patents Act No. 57 of 1978 (as amended) of South Africa a patent “may be granted for any new invention that involves an inventive step and is capable of being used in trade, industry or agriculture”.

South Africa is a signatory to the 1994 Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement by the WTO (World Trade Organization) which aims to standardize the protection of intellectual property rights across member nations including the patenting of pharmaceuticals (Subhan J, 2006).

The governments of participating countries are obligated to meet the following general principles:

- patent protection should be provided to both product and process, allowing certain exceptions
- the period of patent protection should last for 20 years from the date it was filed
- there should be non-discrimination in terms of the place of invention, whether products are locally or internationally produced or regarding the field of technology
- the product or process must meet the three criteria of novelty, non-obviousness and industrial applicability
- disclosure of details of the invention of the patent must be made in the application filed and be made public (WTO, 2006).

Subhan (2006) mentions two provisions of the TRIPs agreement that could be utilized should there be a public crisis:

- (1) Compulsory licencing where a member government is authorized to grant a licence to a party capable of producing the invention under patent without the consent of that patent holder – after reasonable attempts to seek a voluntary licence from the patent holder.
- (2) Parallel importation which allows the South African government to import medicines under patent without authorization from the patent holder into the country should the price be lower elsewhere.

Patents in the pharmaceutical industry are often a controversial topic and there are many differing opinions on the matter.

Craig and Malek (1995) have presented both sides of the argument. Their observation is that innovator pharmaceutical companies have been accused of abusing the patent protection system by creating oligopoly markets and charging exorbitant prices for life-saving medication. The high-risk Research and Development (R&D) that pharmaceutical companies have to sustain is also recognized by the authors. Research and development of medicines is fundamental to the pharmaceutical industry and incurs tremendous expenditure in order to ensure that safe, efficacious medicines of a good quality are introduced on the market. In order to protect their intellectual property, companies patent their active drug substance, formulations and processes. This prevents other (generic) companies – albeit only for a certain amount of time- from copying their intellectual property and manufacturing the same product at a cheaper price.

Bruce Lehman (2003), president of the International Intellectual Property Institute maintains that an effective patent protection is important, especially in developing countries, as it drives the development of life-saving medication. Although the important role of research funded by the public sector is acknowledged, the author is of the opinion that the profit incentive offered through pharmaceutical companies has been the most significant driver of advances in medical science – more than 92% of new medicines were developed by patent dependant pharmaceutical companies by the 1980's.

Many 'blockbuster' drugs – most notably Lipitor[®] (atorvastatin; Pfizer), Zocor[®] (simvastatin; Merck), Seroquel[®] (quetiapine; AstraZeneca) – have come off patent,

and its detrimental effects to the company's bottom line have been widely published. Authors such as Cutler (2007) and Ledford (2011) are of the opinion that the 'blockbuster' model is not sustainable and its time has passed. Harrison (2011) and Service (2004) predict that new strategies employed by innovator companies include focusing on drugs that are being tailored genetically to patients being treated for certain conditions (pharmacogenomics), reformulating existing products into extended release or different dosage forms and mergers and acquisitions with other research companies to boost drying pipelines.

Hudson (2000) analysed the impact of generics in the pharmaceutical market post-expiration of patents in four countries: United States, United Kingdom, Germany and Japan. The findings of this study are in line with previous research in this field and confirm that there is a considerably negative impact on the sales of the original brand after entry of its generics on the market especially if the product was successful and had a large market presence.

The analysis also showed, however, that the value of the patent still continued after its expiration as there was a lag between patent expiry and generic entry and during this period the branded product still held its market share. The loss in sales and market share did not occur instantaneously but rather over a period of time.

Correa (2011) who undertook a study regarding the patent system in five developing countries - Argentina, Brazil, Colombia, India and South Africa believes that the patent system, particularly in South Africa hampers public access to affordable medicines. It was found that the patent system in South Africa differed to the other four countries as patents are issued without substantive examination. Unlike the other countries, South Africa merely registers patents without verifying if it meets the requirements for patentability. Another observation was that there is an increase of "minor, incremental innovations" to existing drugs (formulation, salt, dosage forms, polymorphs) that serves to extend the exclusivity of their medicine, thereby denying generic companies the opportunity to provide cheaper and better access to medicines in these developing countries.

These issues have recently been addressed in a draft National Policy on Intellectual Property which was issued for public comment in September 2013 by the Department of Trade and Industry. The policy aims to introduce patent examination as well as strengthen patent criteria making it difficult to combine previously existing

drugs or adding new indications to medicines currently on the market. Pre- and post-oppositions to patent grants could also be allowed under the new legislation (Department of Trade and Industry, 2013). It is a topic of heated debate between public health activists and innovator drug companies in South Africa and the outcome will have a great impact on the future of healthcare and the pharmaceutical industry.

The economic rationale for the strategy of introducing the pure enantiomer form of the product into the market is that the new, improved drug can be launched and marketed before the patent for the racemate expires – thereby curtailing the success of generic forms of the racemate that will be launched after patent expiry. The market share of the innovator drug is therefore retained in spite of developing generic pressure of the racemate.

Enantiomer patents are often termed “selection patents” as the single enantiomer is derived from the basic patent of the racemate. Enantiomer patents are often challenged on their ‘inventiveness’ – the enantiomer should exhibit pharmacological and/or pharmacokinetic properties that are superior to both the racemate and its corresponding inactive enantiomer at a ratio exceeding 2:1 (Agranat and Wainschein, 2010). This potency ratio between the most active enantiomer (the eutomer) and the less active enantiomer (the distomer), is also known as the eudismic ratio. The ‘Pfeiffer rule’ proposes that the lower the effective dose for a racemic medicine, the greater the difference in the pharmacological effect of the optical isomers (Waldeck, 2003).

Metzke (2010) refers to the subject of enantiomer patenting as “product hopping” that is used by companies to “allow unjustified extensions of market exclusivity” and challenges the validity of these patents based on the obviousness criteria.

3.3 Private versus Public Healthcare Markets in South Africa

South Africa's healthcare industry is made up of the state funded public sector and the private sector where consumers pay with their own earnings, either in cash or through their medical aid.

Medicines for the public sector are sourced from the pharmaceutical industry through the issuing of government tenders for drugs listed on the EDL (Essential Drugs List). It is important to note that Single Exit Price (SEP) does not apply to tenders and tender prices will therefore vary. Medicines on the EDL are intended to address the most prevalent diseases in the population and generics are widely favoured due to the decreased cost. Single enantiomer drugs do not normally feature as they are considered too expensive.

According to IMS data used in the May 2012 Focus report on Pharmaceuticals in South Africa; the Total Pharmaceutical Market was valued at more than R25 billion in November 2011.

The private market is characterized by pharmaceutical companies selling their products to various distributors and then pharmacies at the Single Exit Price (SEP) from which consumers will ultimately buy their medication for cash or through their medical aid. The SEP is adjusted annually by the Minister on recommendation of the Pricing Committee. The percentage increase is based on the average Consumer Price Index (CPI) from the preceding year and foreign exchange rate (Department of Health, 2006). The SEP is then communicated to the pharmaceutical industry by Government Gazette.

This study is based on pharmaceutical sales in the private sector only.

4. AIM

To investigate the impact of the introduction of an enantiomer of an already marketed racemic pharmaceutical product on drug utilization and market share in the private South African pharmaceutical market.

5. OBJECTIVES

The impact of the single enantiomer on drug utilization and market share of the original racemate and of overall utilisation of both products in the private South African pharmaceutical market was measured in the following ways:

1. The volume of units sold of the original racemate and its generics in the year before the single enantiomer was introduced onto the market, the year the single enantiomer was launched and three years after the launch
2. The total market value of each applicable drug that was sold in the year before the single enantiomer was launched, the year the single enantiomer was launched and three years after the launch.
3. The total volume of units sold and sales of both the enantiomer and the racemate products on the market from the innovator company compared to other companies in the total drug molecule market (market share).
4. The differences in company market share year on year as outlined above nationally
5. The probability of the single enantiomer being prescribed over the racemate and its generics year on year.

6. METHODS

6.1 *Data Source*

IMS Health is a global company that provides market-related information and data on prescriptions and sales to the pharmaceutical industry. Permission to access this IMS database has been granted by a pharmaceutical company for the purposes of this research.

A retrospective analysis of the IMS data for drug sales and volume of each single enantiomer in relation to its racemic originator (and generics) in the Total Private Market (TPM) was conducted using Moving Annual Totals (MAT) from a year prior to launch until three years post-launch.

6.2 Data Range

This study focussed on the drug utilization of three different drug substance pairs as outlined in *Table 1*.

Table 1: Drug substance pairs

Racemate	Trade name	Launch Date	Single enantiomer	Trade name	Manufacturer	Launch date
Omeprazole	LOSEC [®]	Feb. 1990	Esomeprazole	NEXIAM [®]	AstraZeneca (Pty) SA	Apr. 2002
Citalopram	CIPRAMIL [®]	Sep. 1994	Escitalopram	CIPRALEX [®]	Lundbeck Pharmaceuticals	June 2004
Cetirizine	ZYRTEC [®]	Jan. 1991	Levocetirizine	XYZAL [®]	UCB Pharma	Aug. 2004

These medicines were initially in the market as racemates and then later, the single enantiomer version of the medicine was launched into the market by the same pharmaceutical company.

These original racemates – omeprazole (LOSEC[®]), citalopram (CIPRAMIL[®]) and cetirizine (ZYRTEC[®]) have since seen the introduction of their generics into the market.

The following generics in *Table 2* were available for the racemates during the study period (2001-2007):

Table 2: Racemates and current generics

Substance	Generic	Manufacturer	Launch date
Omeprazole (LOSEC)	Adco-Omeprazole [®]	Adcock Ingram	Sep. 2004
	Altosec [®]	Aspen	Jan. 2001
	Lokit [®]	Pharmascript	July 2006
	DRL-Omeprazole [®]	Pharmaplan	July 2005
	Omez [®]	Dr Reddy's	July 2004
	Omiloc [®]	Hexal Pharma	Jan. 2005
	Sandoz-Omeprazole [®]	Sandoz	Aug. 2004
	Ulzec [®]	Triomed	± 2000
Citalopram (CIPRAMIL)	Arrow-Citalopram [®]	Arrow	June 2010
	Austell Citalopram [®]	Austell	Dec. 2006
	Cilift [®]	Aspen	May 2003
	Citalo Hexal [®]	Hexal Pharma	March 2005
	Depramil [®]	Cipla Medpro	April 2005
	Sandoz Citalopram [®]	Sandoz	Aug. 2005
	Adco-Talomil [®]	Adcock Ingram	March 2003
	Merck-Citalopram [®]	Merck Generics	April 2006

	Ran-Citalopram [®]	Ranbaxy	Sept. 2005
	Cilate [®]	Unicorn/ Betabs	May 2007
Cetirizine (ZYRTEC)	Adco-Cetirizine [®]	Adcock Ingram	Aug. 2004
	Allecet [®]	Cipla Medpro	June 2004
	Allermine [®]	Merck Generics/Mylan	Oct. 2004
	Aspen Cetirizine [®]	Aspen	April 2005
	Austell Cetirizine [®]	Austell	April 2005
	Betek [®]	Be-Tabs	March 2007
	Sandoz Cetirizine [®]	Sandoz	Aug. 2004
	Cetirizine Hexal [®]	Sandoz	Oct. 2004
	Texa [®]	Pharma Dynamics	March 2003
	Zyncet [®]	Sekpharma	Jan. 2006
	UCB Cetirizine [®]	UCB Pharma	May 2003

(IMS, 2013)

IMS data was collected to analyse:

1. The drug utilization and market share of the original racemate and its generics (Table 2 above) according to the volume of products sold as well as rand value of products sold the year prior to the introduction of the new single enantiomer version onto the market.
2. The drug utilization and market share of the single enantiomer drug compared to its racemates in the year the single enantiomer was launched according to the volume of products sold and rand value.
3. Year on year differences in drug utilization and changes in company market share since the introduction of the single enantiomer onto the market until three years post-launch.
4. Impact on the total volume and sales of both the enantiomer and the racemate products of the innovator company on the market (i.e. did it result in further market share for the company).
5. The probability of the single enantiomer being prescribed/sold over the racemate and generics year on year.

Exclusions to the data range procured from the IMS database are as follows:

- Only the oral dosage form of esomeprazole and omeprazole (plus its generics) were used in this study. The intravenous (IV) dosage form has different indications for use and consequently is only used in a hospital setting.

- Only drug molecules identical to the originator molecule were analysed as opposed to all drug molecules belonging to the drug class (e.g. Proton Pump Inhibitors (PPIs), Selective Serotonin Reuptake Inhibitors (SSRIs) or H₁-receptor antagonists).

The single enantiomer version of citalopram, escitalopram (CIPRALEX[®]) has also come off patent. The generics currently available for escitalopram (CIPRALEX[®]) are presented in *Table 3*:

Table 3: Escitalopram Generics

Substance	Generic	Manufacturer	Launch Date
Escitalopram (CIPRALEX [®])	Aspen Escitalopram [®]	Aspen	Aug. 2009
	Citraz [®]	Dr Reddy's	Nov. 2008
	Lexamil [®]	Cipla Medpro	May 2008
	Mylan Escitalopram [®]	Mylan	March 2010
	Zytomil [®]	Pharma Dynamica	Dec. 2010
	Escitalopram Be-Tabs [®]	Ranbaxy	April 2011

(IMS, 2013)

A secondary analysis of escitalopram was conducted to determine the impact on drug utilization and market share once the single enantiomer drugs are also exposed to generic pressure.

6.3 Data Management

Information was extracted from the IMS database and exported to a Microsoft Excel spreadsheet (*Appendix 1*).

This Microsoft Excel sheet contained the following the headings:

- Drug Class
- Dosage form
- Name of Molecule
- Name of Brand
- Manufacturer name
- Launch Date

- Pack size and Strength
- Number of Units sold (Volume) per month
- Rand value of sales per month
- Price per unit pack size per month

The annual Single Exit Price (SEP) increases have been applied to the data and the sales figures were automatically adjusted to reflect this. The pricing figures presented do not include dispensing fees.

6.4 Statistical Analysis

Microsoft Excel and data analysis and statistical software – IBM Statistical Package for Social Sciences (SPSS) Version 21.0 - was used to analyse the data collected.

The descriptive statistical analysis included:

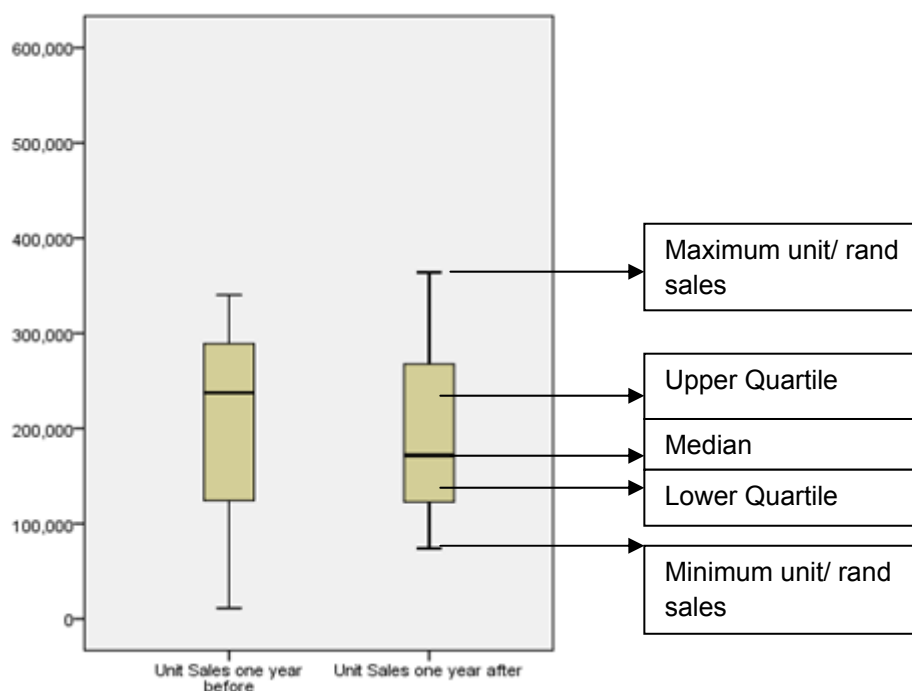
1. Line graphs of each different single enantiomer based pharmaceutical product in relation to the originator racemate and its generics were plotted with time on the x-axis and volume of units sold on the y-axis to show the trend in drug utilization.
2. Line graphs with time plotted on the x-axis and the rand value of sales on the y-axis to show the trend in sales of each applicable drug.

A Moving Annual Total was used to smooth out the fluctuations so that the underlying direction of the trend could be determined.

3. Market share (in both unit sales and rand value of sales) of the single enantiomer, originator racemate and its generics is expressed in pie charts illustrating each company's contribution to the Total Private Market (TPM).
4. Box and whisker plots of the racemate and its generics have been plotted for the year before the single enantiomer was launched, the year after its launch, two years after launch and three years after launch.

Box and whisker plots graphically display distribution of data. In this study they are used to visually show the impact of the single enantiomer on the rand

and unit sales of the racemate and generics that were on the market before the single enantiomer product was launched. The whiskers (lines) represent the maximum and minimum unit sales/ rand sales. The box represents the interquartile range which is divided by the median line into the upper quartile and lower quartile.



To ascertain the impact the single enantiomer made on the market, the data set used excluded not only the single enantiomer but also any racemates and generics launched after the introduction of the single enantiomer. This gives a true reflection of what impact the single enantiomer made to the existing market.

Due to the small population size, the mean can be distorted by one or two observations where the volume of unit sales or value of rand sales were exceptionally high or low - it was therefore more appropriate to use the median when there was skewness observed in the data.

In addition, the following inferential statistical method was applied to the data:

1. Probability

Probability is defined by Olofsson (2005) as the “mathematics of randomness” and is a method of predicting an outcome where there are uncertainties. This

study makes use of objective or experimental probability where the relative frequency of a certain event occurring is measured by the formula:

$$f_n = \frac{S_n}{n}$$

Where f_n is the relative frequency, S_n is the number of times the event occurred, and n is the total number of outcomes (Olofsson, 2005).

The probability of the enantiomer being prescribed/ sold instead of the racemate at different time points namely, the year the single enantiomer was launched and then one, two and three years post launch has been calculated using the following formula:

$$\frac{\text{Units of Single Enantiomer (SE) sold 1/ 2/ 3 year(s) after launch}}{\text{Total units of SE + Racemates sold 1/ 2/ 3 year(s) after launch}}$$

The probability of the single enantiomer being prescribed or sold increases as the probability percentage increases.

This calculation demonstrates whether the drug utilization of the single enantiomer increased or decreased from introduction until three years subsequent to its launch.

6.5 Study Limitations

The IMS database reflects the private sector only and is therefore a limitation to the scope of this study.

Drug molecules identical to the originator molecule were analysed as opposed to all drug molecules belonging to the drug class (e.g. Proton Pump Inhibitors (PPIs), Selective Serotonin Reuptake Inhibitors (SSRIs) or H₁-receptor antagonists).

IMS data further back than November 2001 could not be accessed; consequently, values were annualized for omeprazole data a year before launch (2002) where statistical comparisons were made using annual totals.

The influence of marketing strategies that could have been employed to prescribers and/or consumers was not investigated for the purposes of this study.

7. RESULTS

7.1 Omeprazole-Esomeprazole Case Study

7.1.1 Entry of Esomeprazole onto Market

The originator molecule, LOSEC[®] MUPS launched in February 1990 dominated the market prior to the launch of NEXIAM[®] launched in April 2002 by the same pharmaceutical manufacturer – AstraZeneca Pharmaceuticals (Pty) Ltd.

It is clear from *Figure 5* that after the launch of the esomeprazole molecule (NEXIAM[®]) on the market there was a steady increase in the volume of prescriptions written in favour of esomeprazole.

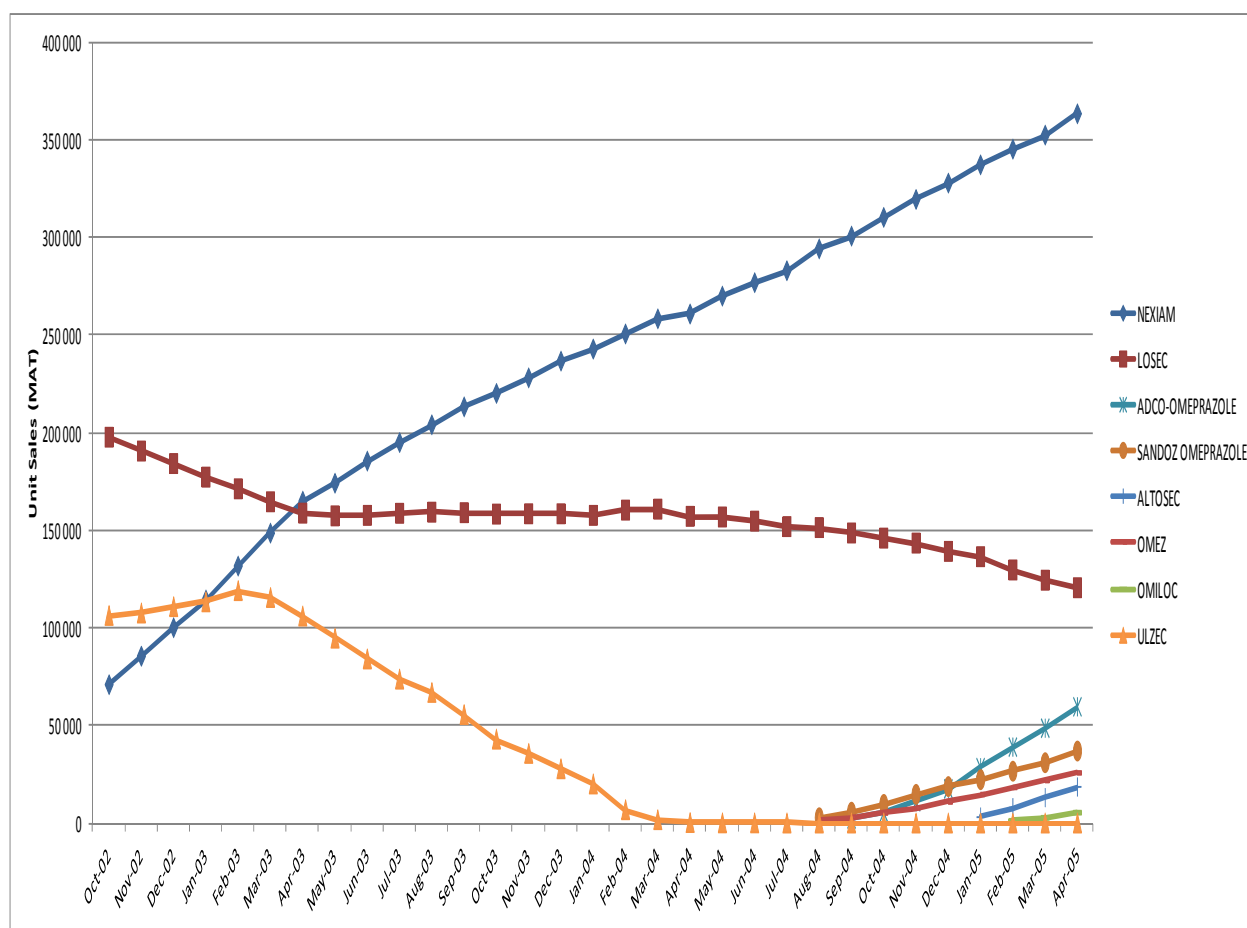


Figure 5: Impact of esomeprazole (NEXIAM[®]) on unit sales in omeprazole market

The introduction of omeprazole generics such as ADCO-OMEPRAZOLE[®], SANDOZ OMEPRAZOLE[®] and OMEZ[®] in early 2004 saw a decrease in both unit and a rand sale for LOSEC[®] but there was still a steady increase of NEXIAM[®] sales.

Interesting to note here is the presence of ULZEC[®], another omeprazole product, launched while LOSEC[®] was still under patent. This alleged violation on patent right was challenged by AstraZeneca and lost. An appeal to this decision was made to the Supreme Court of Appeals of South Africa in September 2002 (The Supreme Court of Appeal of South Africa, Case 63/2002) and the final judgement ruled that there was indeed an infringement on the patent and Triomed Pty (Ltd) was ordered to cease the sale of ULZEC[®] – not before they had succeeded in taking a substantial market share.

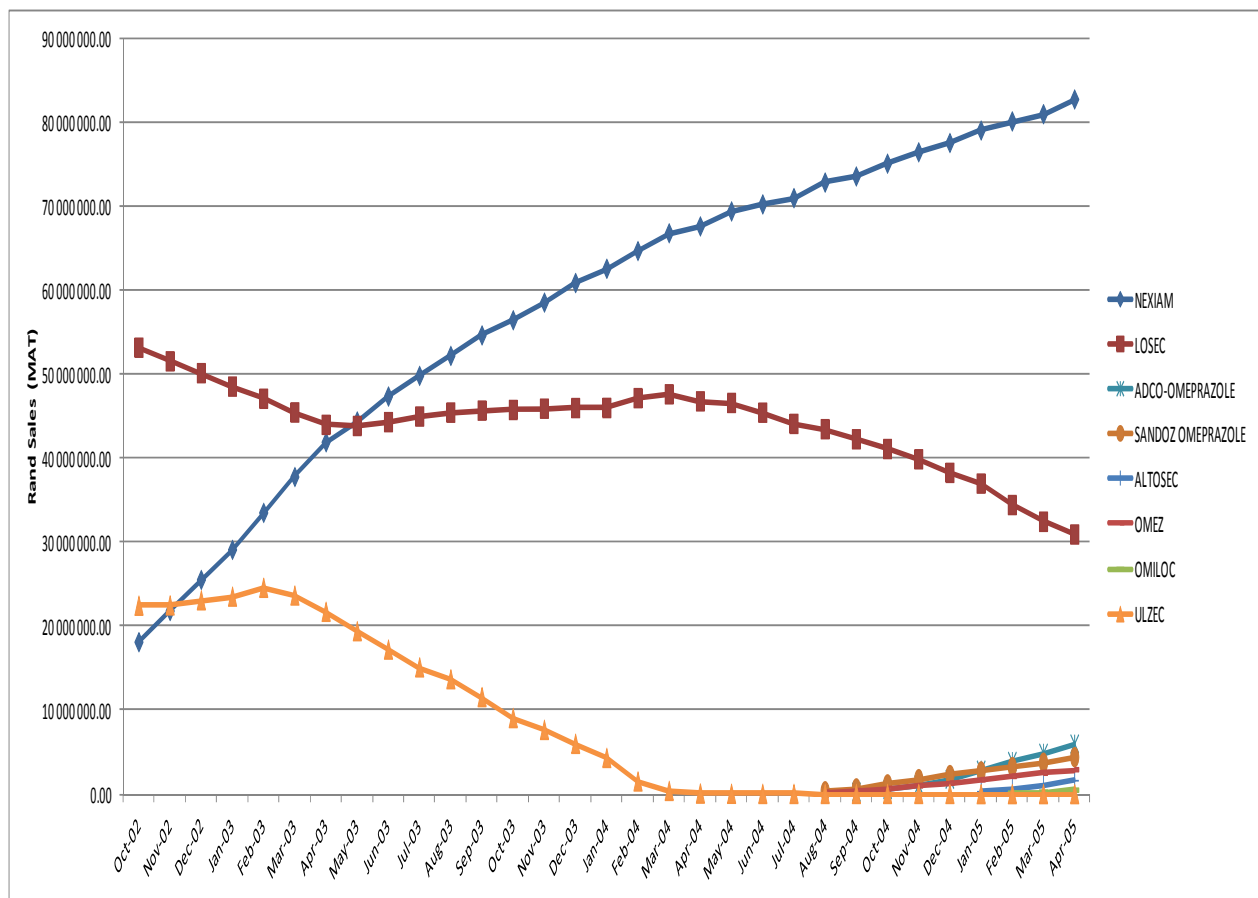


Figure 6: Impact of esomeprazole (NEXIAM[®]) on rand sales in omeprazole market

7.1.2 Impact of Esomeprazole on Market Share

Triomed's launch of ULZEC[®] saw the company gain approximately a quarter of the omeprazole market from AstraZeneca in both rand sales and units in the year before the launch of NEXIAM[®]. This stayed steady until the end of the first year post launch.

The withdrawal of ULZEC[®] from the market allowed AstraZeneca to claim almost the entire market share of the omeprazole/esomeprazole market by the end of the second year. It was only during the third year after the launch of the single

enantiomer, NEXIAM[®], that five other pharmaceutical companies launched generics of the racemate, omeprazole, onto the market. The entry of these products reduced AstraZeneca's market share by 23% in unit sales and only 12% in rand sales.

Unit sales

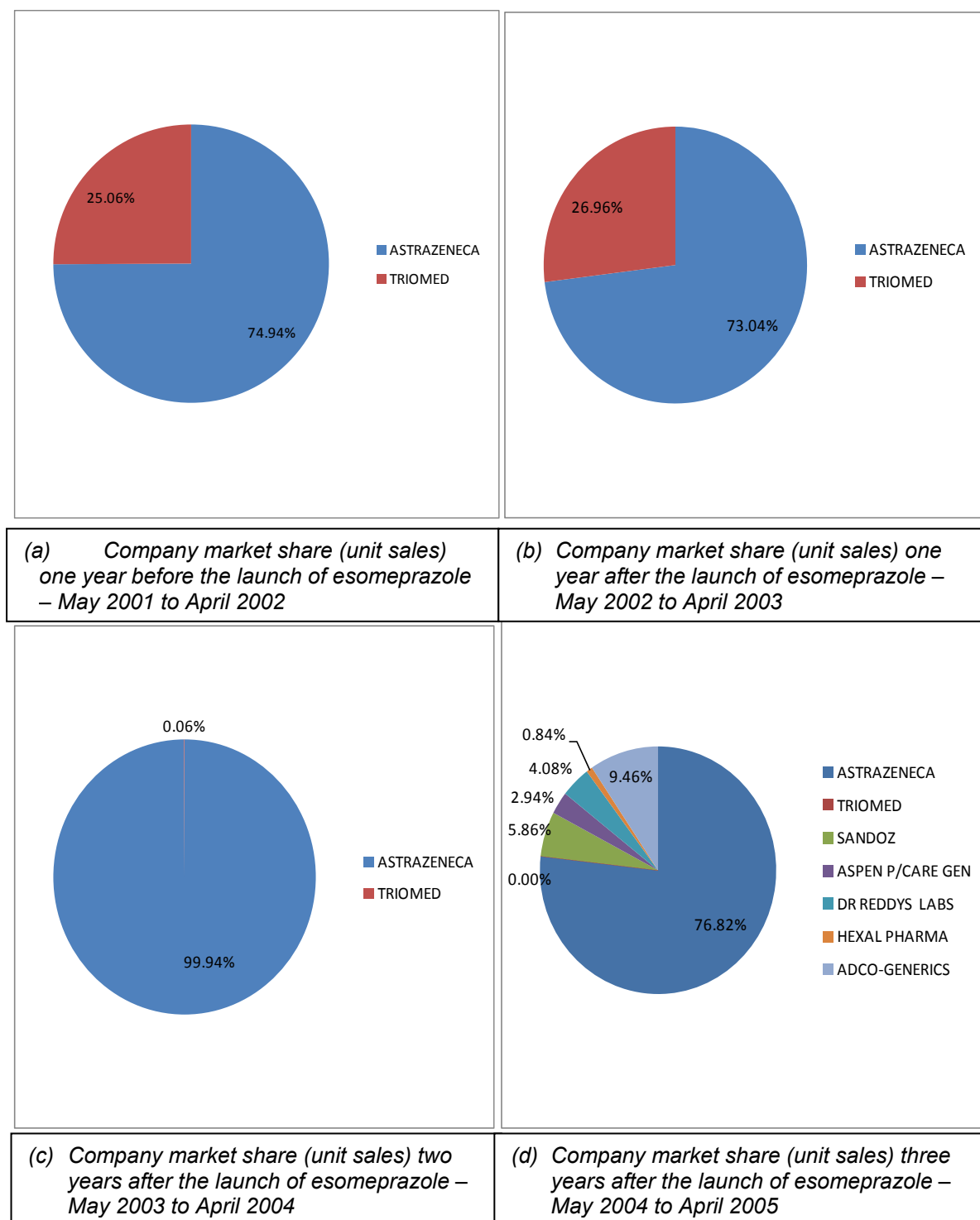


Figure 7: Impact of esomeprazole on market share (Unit sales)

Rand sales

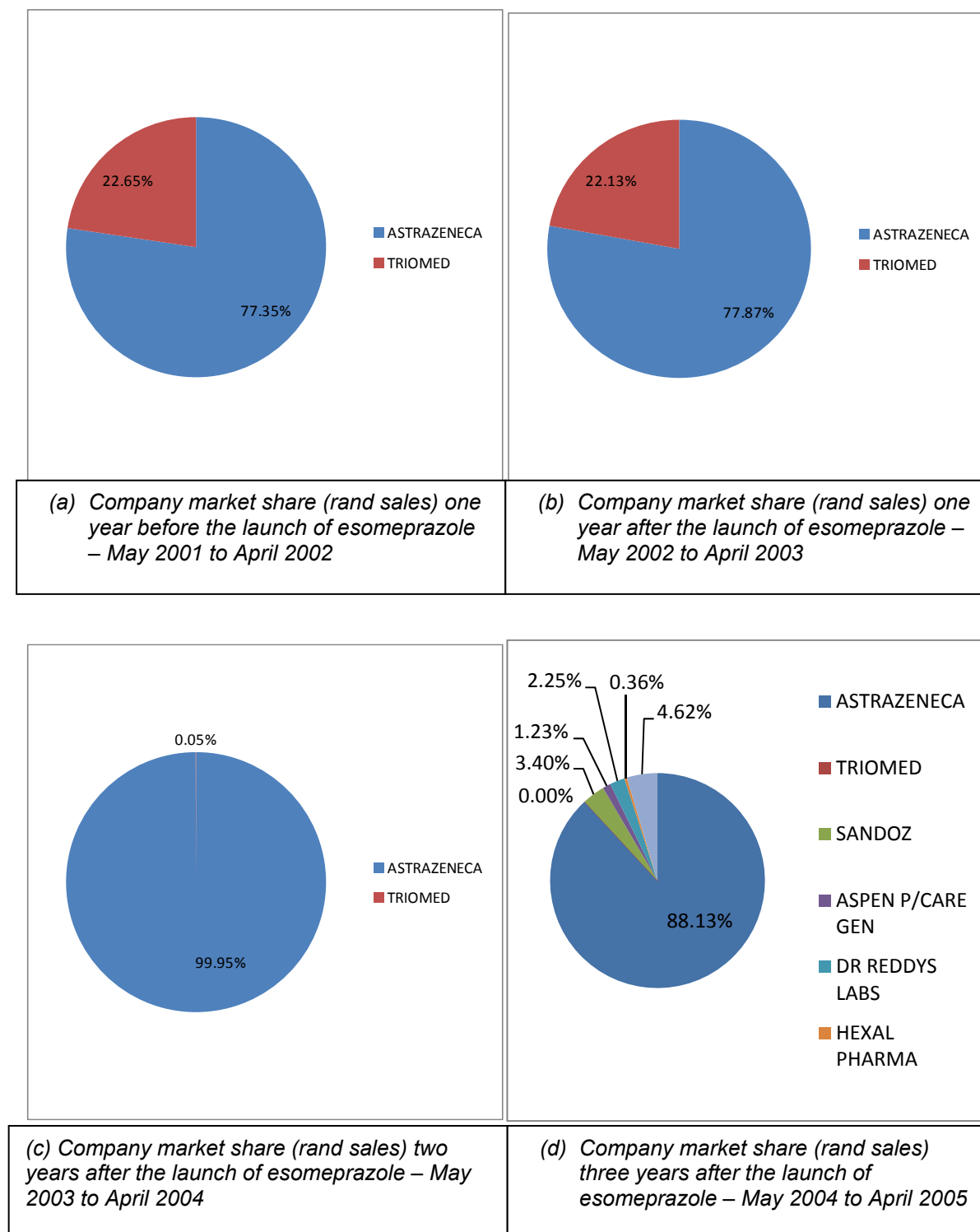


Figure 8: Impact of esomeprazole on market share (Rand sales)

7.1.3 Impact of Esomeprazole on Existing Racemates

Figure 9 and 10 represent the existing omeprazoles on the market before the launch of NEXIAM[®] which consisted only of ULZEC[®] and LOSEC[®]. The median of unit and rand sales increased one year after the launch of the single enantiomer and then fell dramatically to zero after three years post-launch.

This does not represent an organic decline in drug utilization and sales by consumers of the racemate but rather the result of the patent infringement lawsuit that was on-going at the time.

Unit Sales

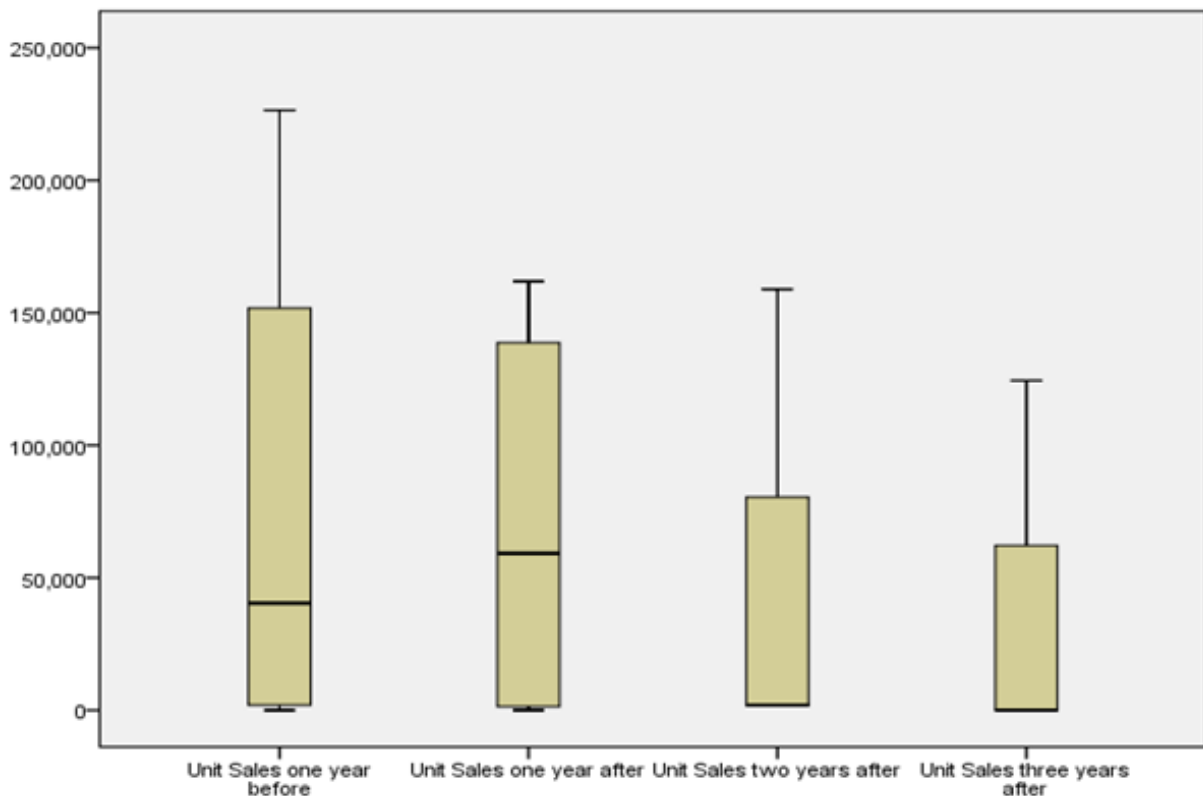


Figure 9: Impact of esomeprazole on existing racemates (Unit sales)

Rand sales

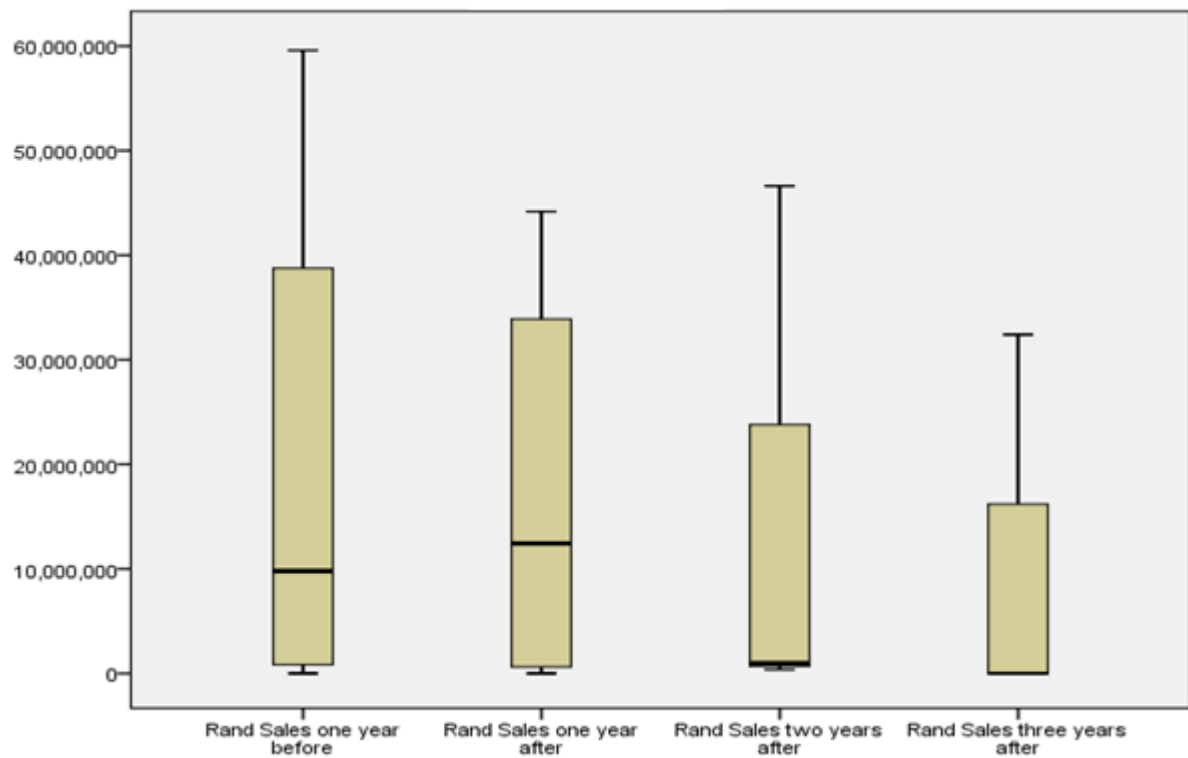


Figure 10: Impact of esomeprazole on existing racemates (Rand sales)

7.1.4 Probability of Esomeprazole being Prescribed or Sold after Launch Compared to Total Omeprazole/ Esomeprazole Market

The proportion of esomeprazole (single enantiomer) units sold of the total molecule market (single enantiomer, racemate and generics) is compared year on year to determine if there was an increase or decrease of use of esomeprazole since its launch into the market.

Table 4: Probability of esomeprazole being prescribed or sold after launch compared to total omeprazole/ esomeprazole market

Probability of SE prescribed year after launch	Probability of SE prescribed two years after launch	Probability of SE prescribed three years after launch
34.6%	61.4%	59.3%

The probability that doctors prescribed esomeprazole in favour of any of the other racemates increased by 26.8% between the first and second years after NEXIAM[®] was launched. The probability took a slight dip of 2.1% in the third year post-launch.

See Appendix 2 for more details

7.2 Citalopram-Escitalopram Case Study

7.2.1 Entry of Escitalopram on the Market

CIPRAMIL[®], the originator citalopram racemate, had already come off patent and was under huge generic pressure from CILIFT[®] and ADCO-TALOMIL[®] when the escitalopram medicine (CIPRALEX[®]) was launched in June 2004.

CILIFT[®] continued to dominate the market and surpass not only CIPRAMIL[®] unit sales but also the growing CIPRALEX[®] product.

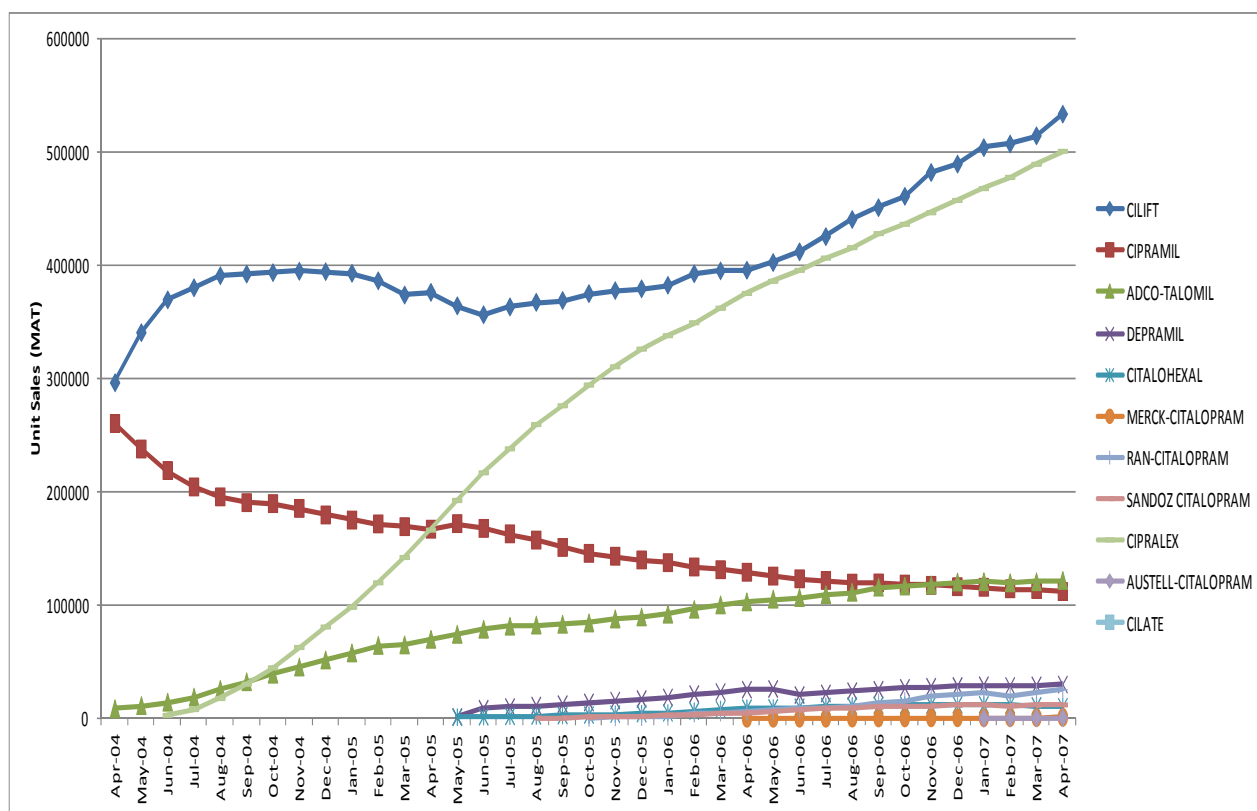


Figure 11: Impact of escitalopram (CIPRALEX®) on unit sales in citalopram market

CILIFT®, manufactured and marketed by Aspen, had the largest volume of units sold but as can be seen from the graph above, their unit sales decreased when CIPRALEX® came onto the market. An analysis of CILIFT®'s unit price provides an explanation: A pack of 30 x CILIFT® 20 mg tablets were initially launched into the market at R152.00 in May 2003. The price per unit pack steadily decreased from May 2004 until it reached a price of just R43.80 per pack by November 2005. They therefore sold the largest volume of units in this period but because of the substantial dropping of their price their unit sales plummeted.

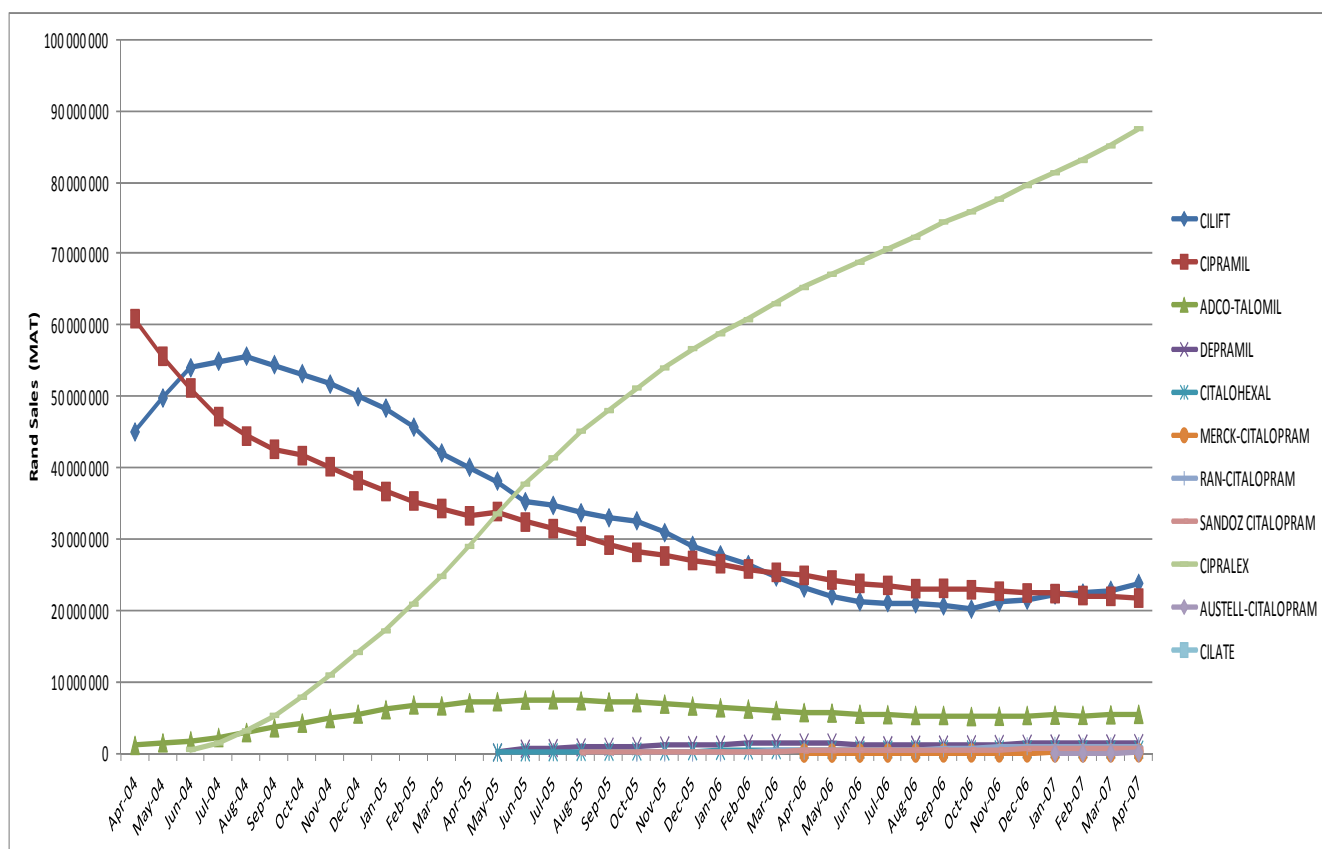


Figure 12: Impact of escitalopram (CIPRALEX®) on rand sales in citalopram market

7.2.2 Impact of Escitalopram on Market Share

In the year before escitalopram was launched, Lundbeck had 40% of market share in terms of units sold and 52% of rand sales in the market. Its closest generic competitor was Aspen who had a share of 58% in terms of units but just 47% of the rand sales in the citalopram market.

The launch of the single enantiomer proved to be very successful for Lundbeck. With the addition of CIPRALEX® to its portfolio, Lundbeck was able to secure 5% more of the market share in units and its rand sales in the market increased by 8% at the end of its first year of launch.

After the second year of escitalopram's entry on the market, Lundbeck had a considerable market share with 75% of rand sales.

Lundbeck continued to lead the market the following year, increasing a further 2% in rand sales to gain 77% of the market share.

Unit sales

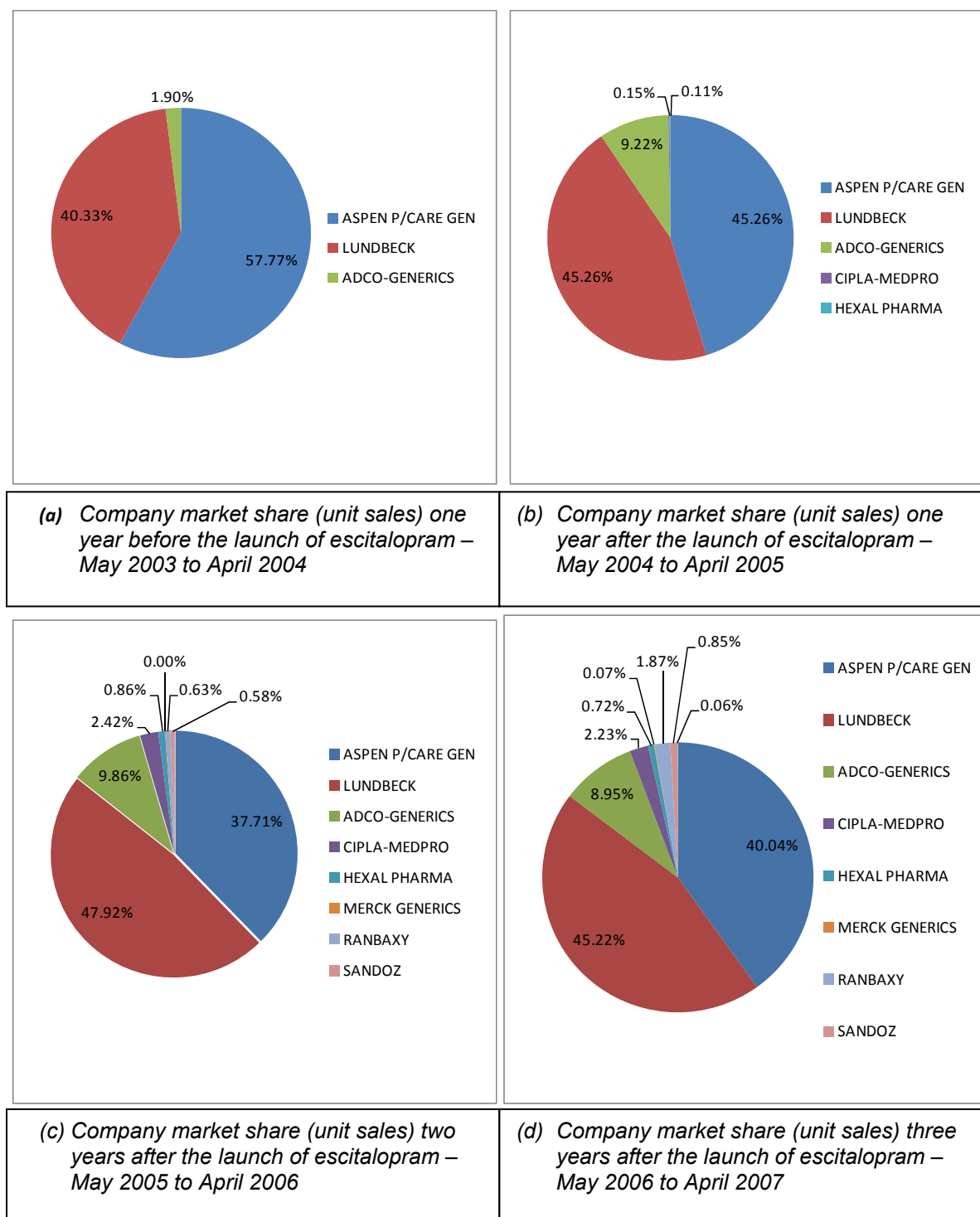


Figure 13: Impact of escitalopram on market share (Unit sales)

Rand Sales

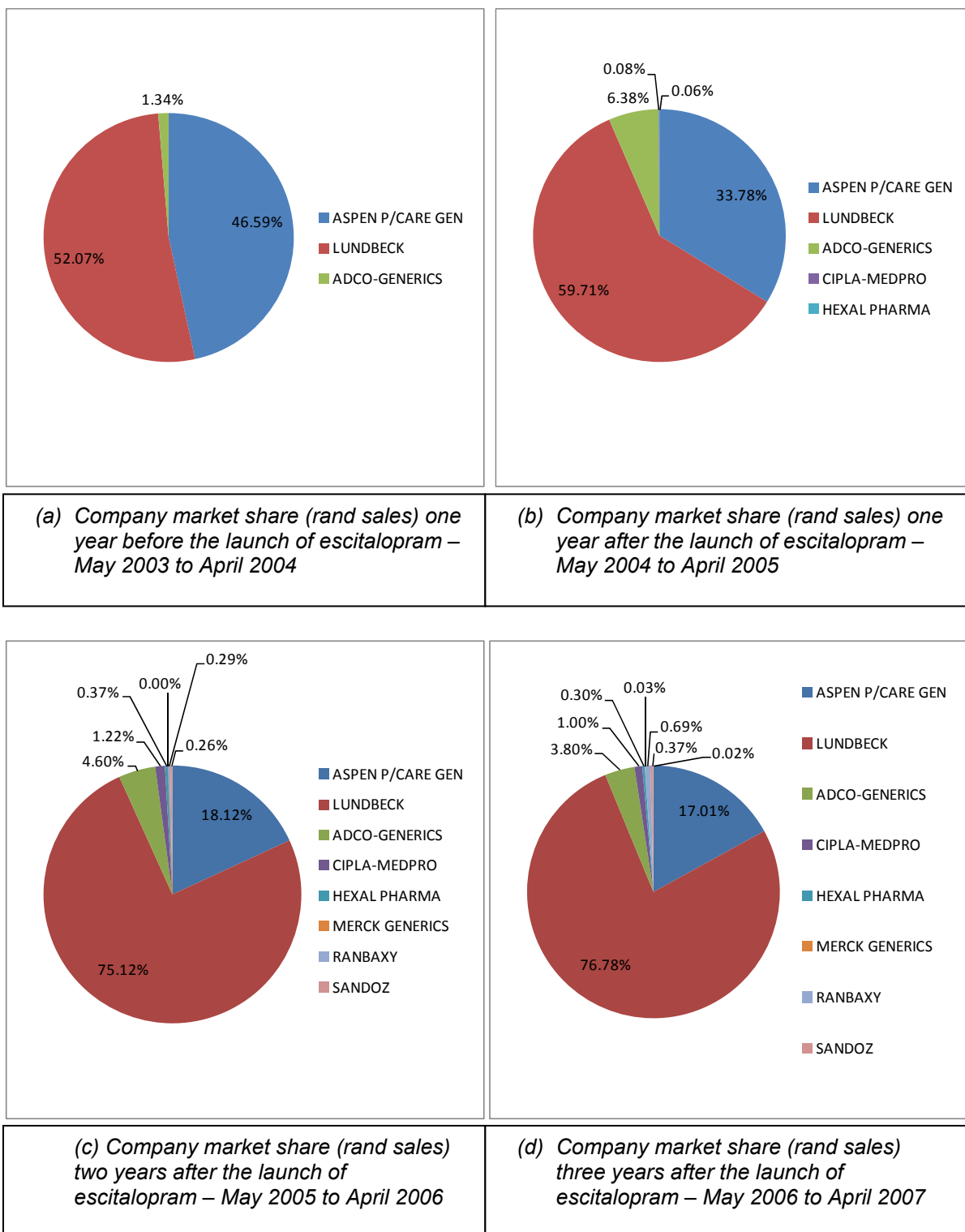


Figure 14: Impact of escitalopram on market share (Rand sales)

7.2.3 Impact of Escitalopram on Existing Racemates

There were three racemates that were on the market prior to the launch of escitalopram. The three racemates represented in Figure 15 and 16 are: CLIFT[®], CIPRAMIL[®] and ADCO-TALOMIL[®]. The launch of the single enantiomer caused a steady decrease in the median of both unit sales and rand sales which levelled off marginally between the second and third year post-launch of the single enantiomer.

It is interesting to note that the maximum unit sales for the racemates continued to grow through the study period. The minimum unit sales also increased.

There was a very large difference between the minimum rand sales and the median in the year before launch of CIPRALEX[®], the single enantiomer. This gap was reduced in the year post launch as the median decreased and the minimum rand sales picked up. The median fell further in the second year and held steady until the third year.

Unit Sales

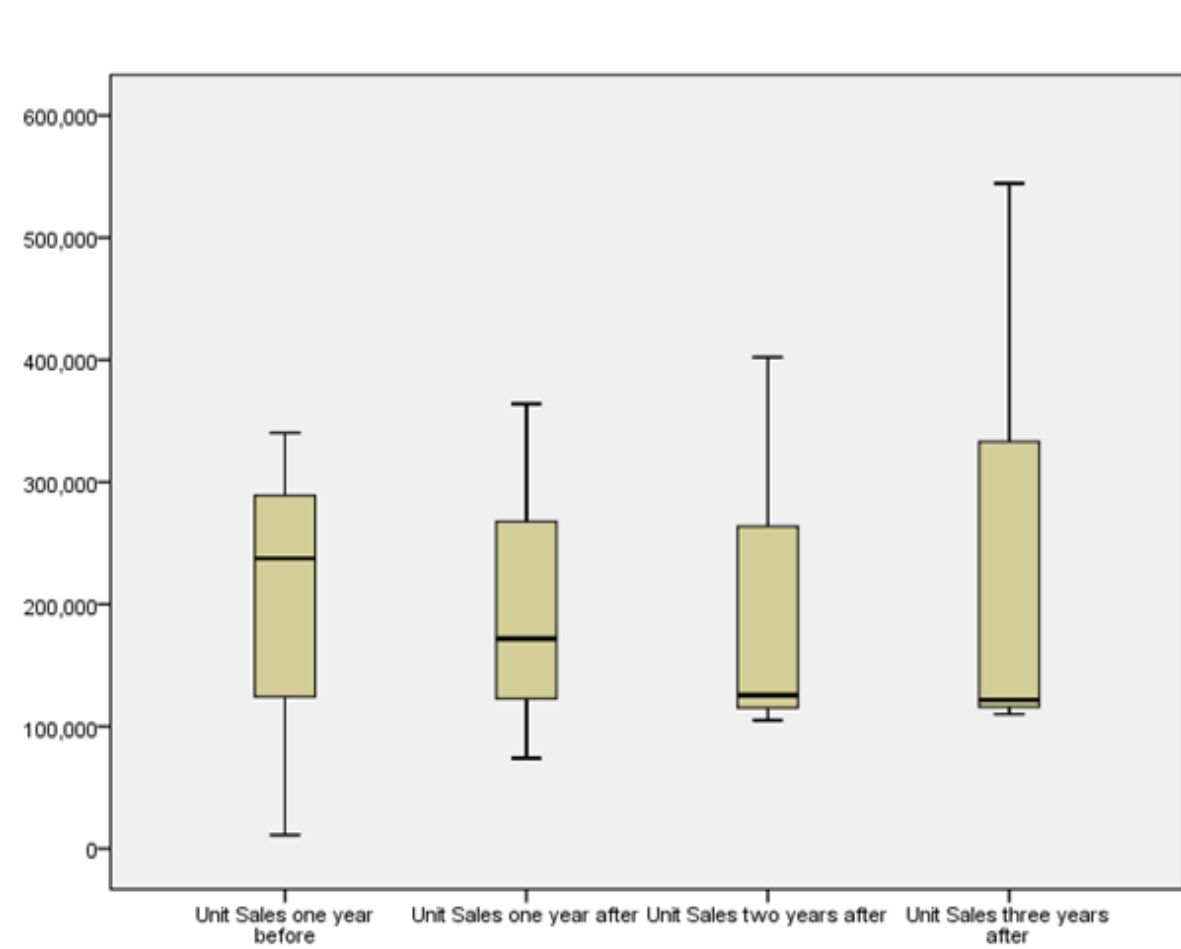


Figure 15: Impact of escitalopram on existing racemates (Unit sales)

Rand Sales

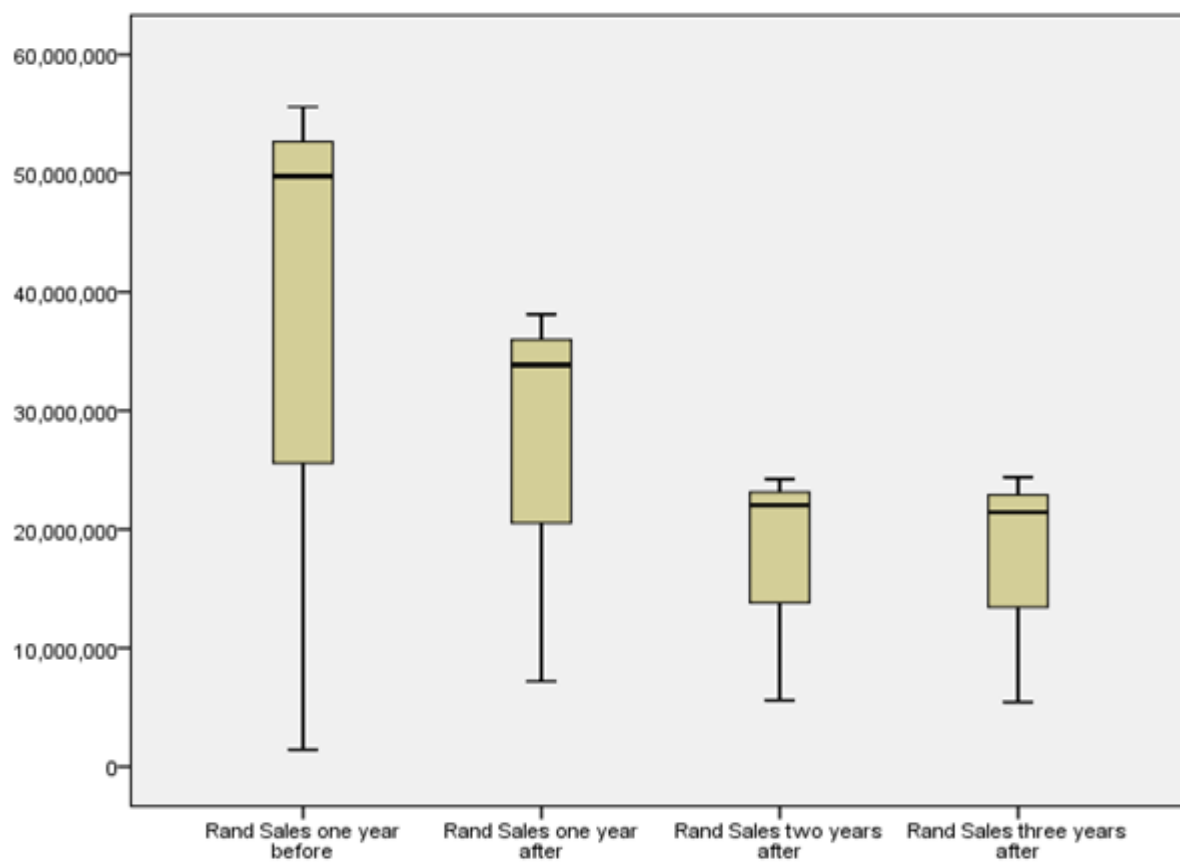


Figure 16: Impact of escitalopram on existing racemates (Rand sales)

7.2.4 Probability of Escitalopram being Prescribed or Sold after Launch Compared to Total Citalopram/ Escitalopram market

There seemed to be a gradual increase in the probability of the single enantiomer CIPRALEX[®] being prescribed through the study period over the racemic citalopram products.

Table 5: Probability of escitalopram being prescribed or sold after launch compared to total citalopram/ escitalopram market

Probability of SE prescribed year after launch	Probability of SE prescribed two years after launch	Probability of SE prescribed three years after launch
23.9%	36.2%	37.1%

See Appendix 2 for more details

7.2.5 Secondary Analysis:

What Happens to the Single Enantiomer Product Once there is Generic Entry

In May 2008, Cipla Medpro launched LEXAMIL[®], a generic version of Lundbeck's CIPRALEX[®] that was still under patent. Cipla Medpro argued the validity of Patent 89/4476 citing lack of novelty, obviousness and insufficiency. Lundbeck's appeal included a proposal to amend claims stated in its patent and for an interdict to stop Cipla Medpro from continuing with their intended launch. On 20th June 2008 in the Court for the Commissioner of Patents, the presiding judge ruled that the patent could not be amended at such a late stage and the application for the interdict was dismissed (Court for the Commissioner of Patents, Case 89/4476).

LEXAMIL[®] was therefore able to continue being marketed and sold by Cipla Medpro much to the detriment of CIPRALEX[®] unit and rand sales, the results of which are evident in *Figure 17* and *Figure 18* below.

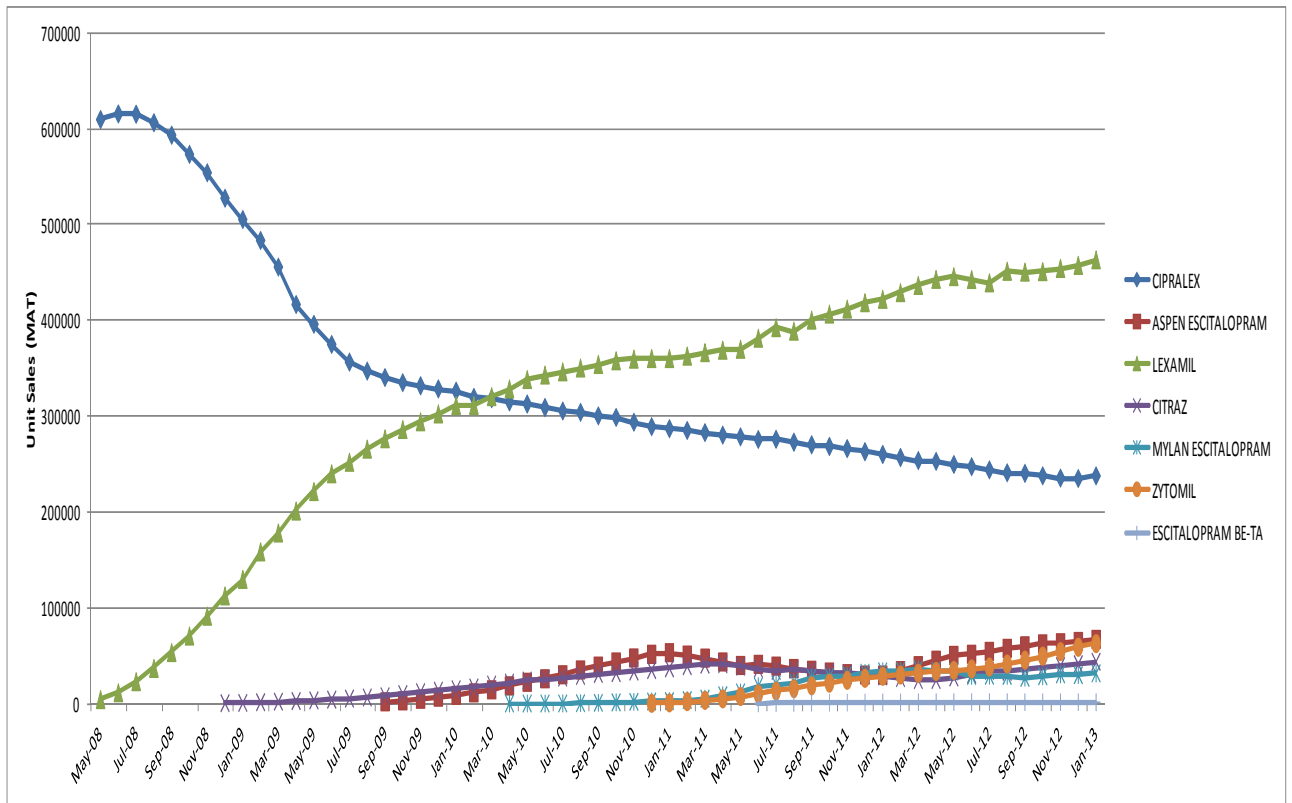


Figure 17: Impact of escitalopram generic entry on CIPRALEX® unit sales

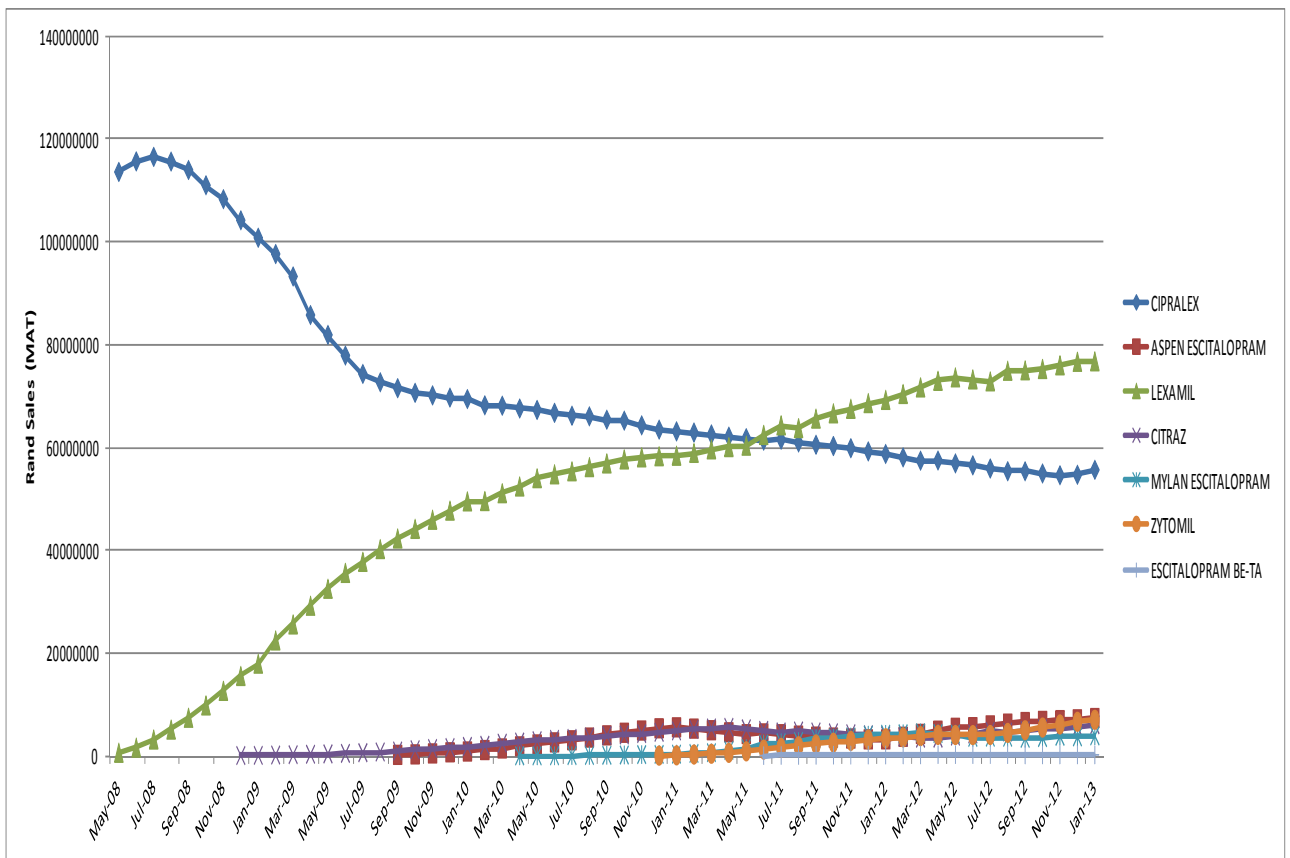


Figure 18: Impact of escitalopram generic entry on CIPRALEX® rand sales

CIPRALEX[®] continued to be a blockbuster drug for its innovator company, Lundbeck, until the end of April 2008. Following the court dismissal of Lundbeck's application to prevent Cipla from launching its escitalopram generic, the monopolistic market share Lundbeck held of the escitalopram market quickly diminished.

After the first year of launch of LEXAMIL[®], Cipla took 32% of unit sales and a 25% of rand sales away from Lundbeck.

At the end of the second year after the patent for escitalopram was invalidated, two more generics manufactured by Dr Reddy's and Aspen Pharmacare was launched. Cipla, however, continued to show steady growth in the market with 48% of unit sales and 42% of rand sales.

The following year, many other generics entered the escitalopram market – Cipla's LEXAMIL[®] was still a firm favourite, with just under half (49%) of the total units of escitalopram sold and 45% of the rand sales. Lundbeck's unit sales and rand sales decreased to 38% and 46% respectively.

Lundbeck's market share continued to plunge under generic competition by the end of the fourth year resulting in just 30% of the total units of escitalopram sold and 39% of the total rand sales in the market.

Unit sales

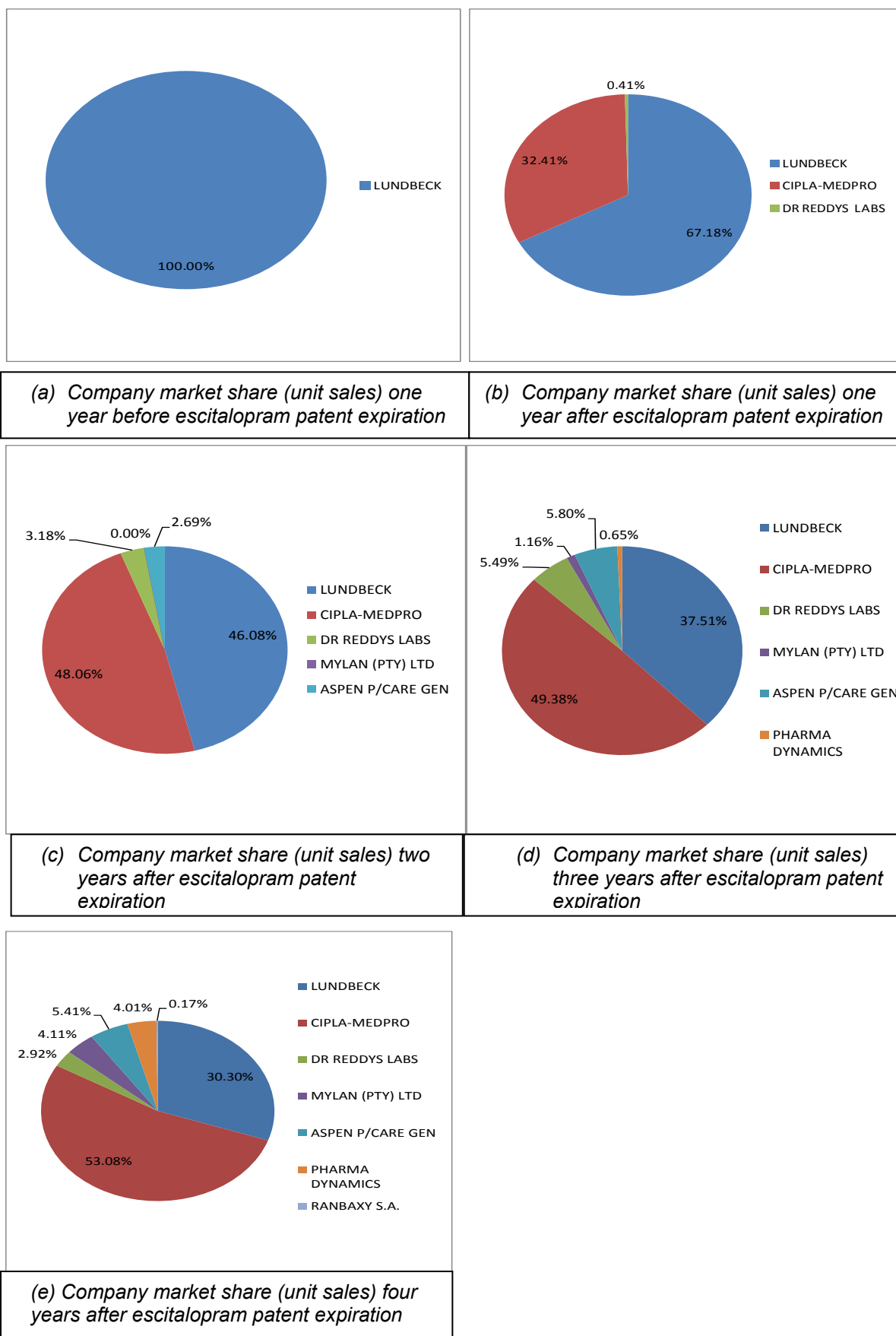


Figure 19: Impact of generic entry on market share after patent expiry of escitalopram (Unit sales)

Rand Sales

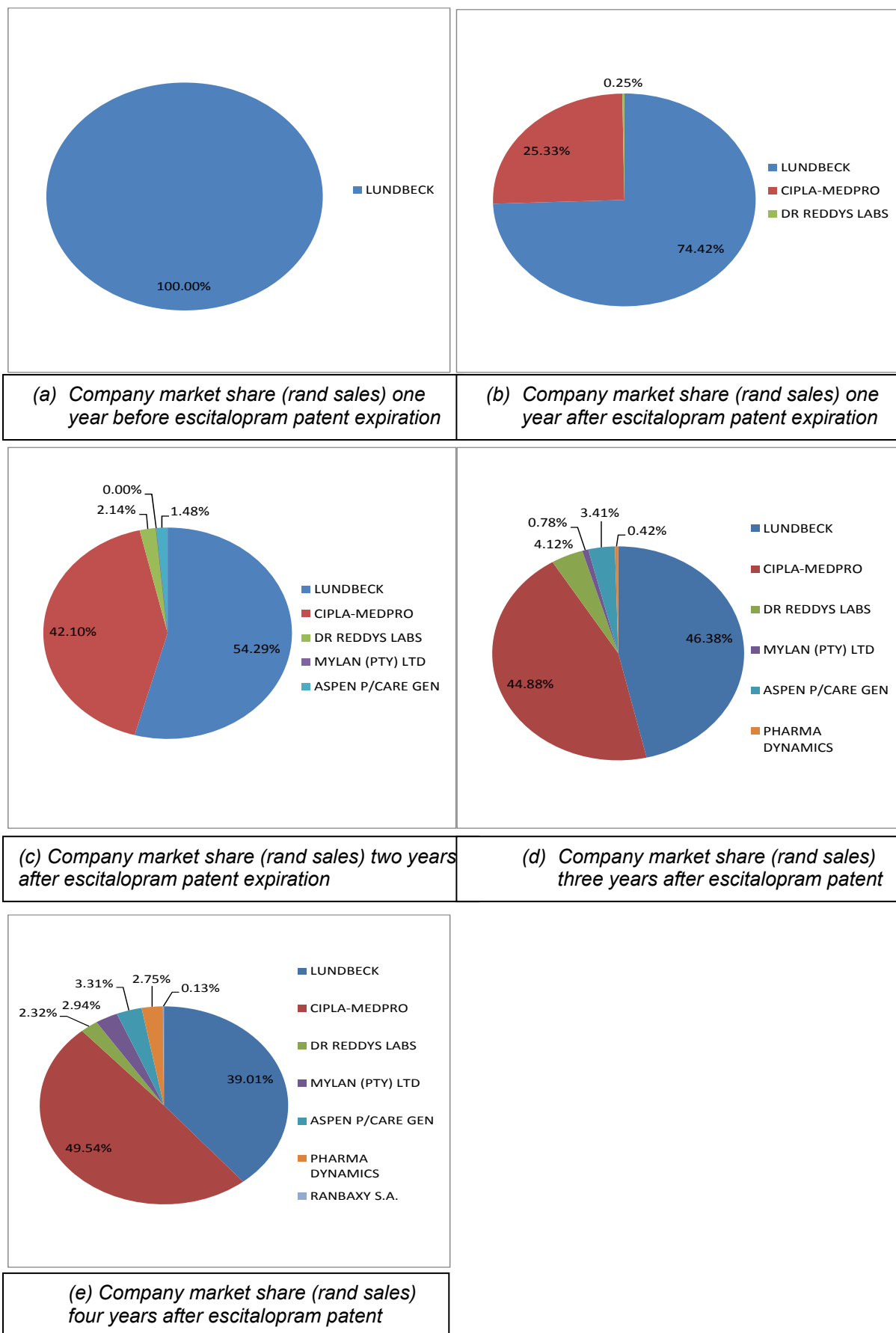


Figure 20: Impact of generic entry on market share after patent expiry of escitalopram (Rand sales)

7.3 Cetirizine-Levocetirizine Case Study

7.3.1 Entry of Levocetirizine on the Market

In contrast to the preceding two examples of prescription medications, the over-the-counter (OTC) market shows more variation between the different brands.

The number of units sold of ZYRTEC[®], the original racemate product, dropped upon the arrival of the single enantiomer, XYZAL[®], into the market in August 2004.

TEXA[®] (a cetirizine generic), however, grew in unit sales during the review period. A possible reason for this can be attributed to the decrease in its purchase price making it more affordable and attractive to the consumer. A pack of 30 x 10 mg tablets was sold at R89.12 when it was first released on the market in March 2003 – this price decreased to just R32.63 – less than half its original value by February 2007. This also explains why the rand sales graph below shows a dip for TEXA[®] sales in spite of the growth of its sales in unit packs.

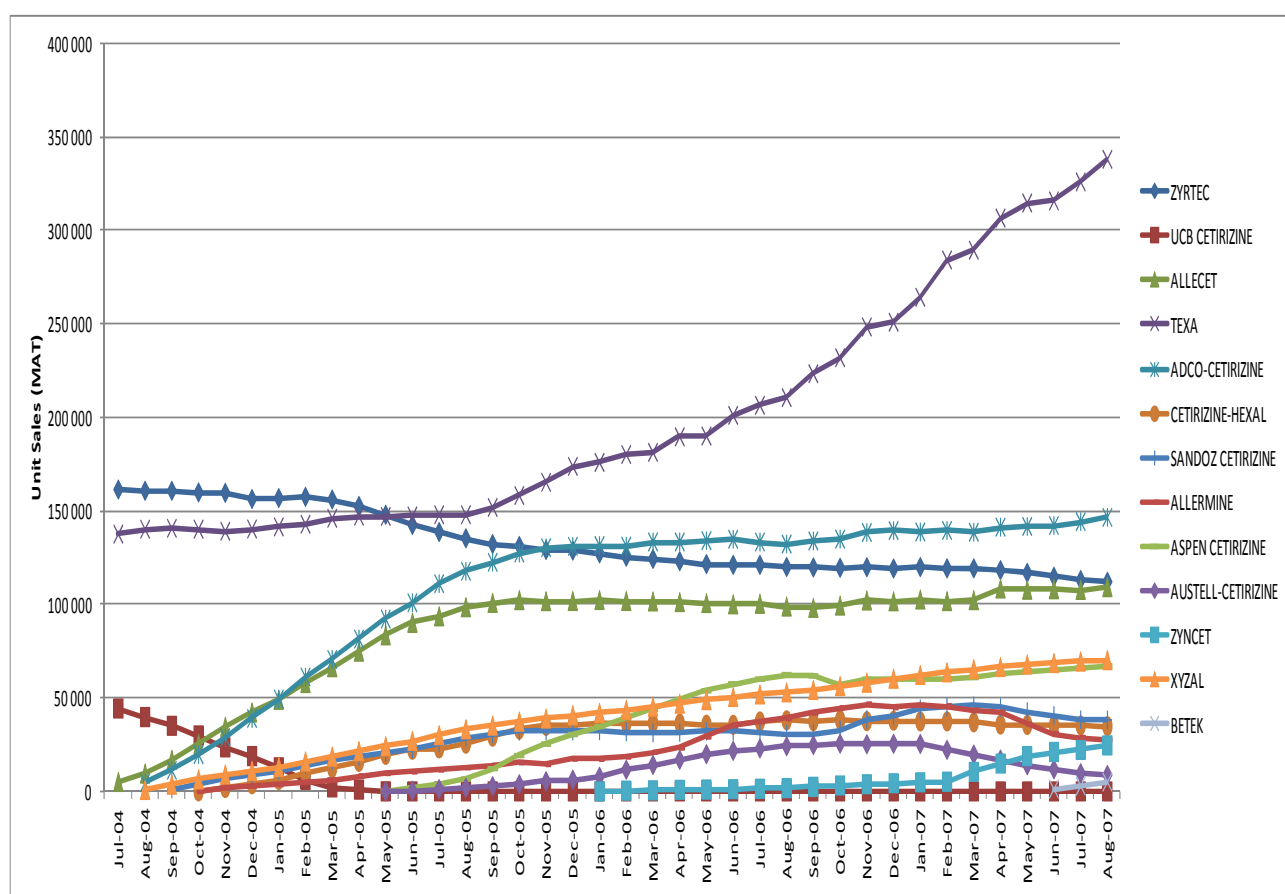


Figure 21: Impact of levocetirizine (XYZAL[®]) on unit sales in cetirizine market

ZYRTEC® experienced a large drop in sales when XYZAL®, its single enantiomer counterpart from the same innovator company (UCB Pharma) was launched.

XYZAL® showed steady growth in the three years following its launch, overtaking the leading cetirizine generic, TEXA®, in rand sales but not in unit sales.

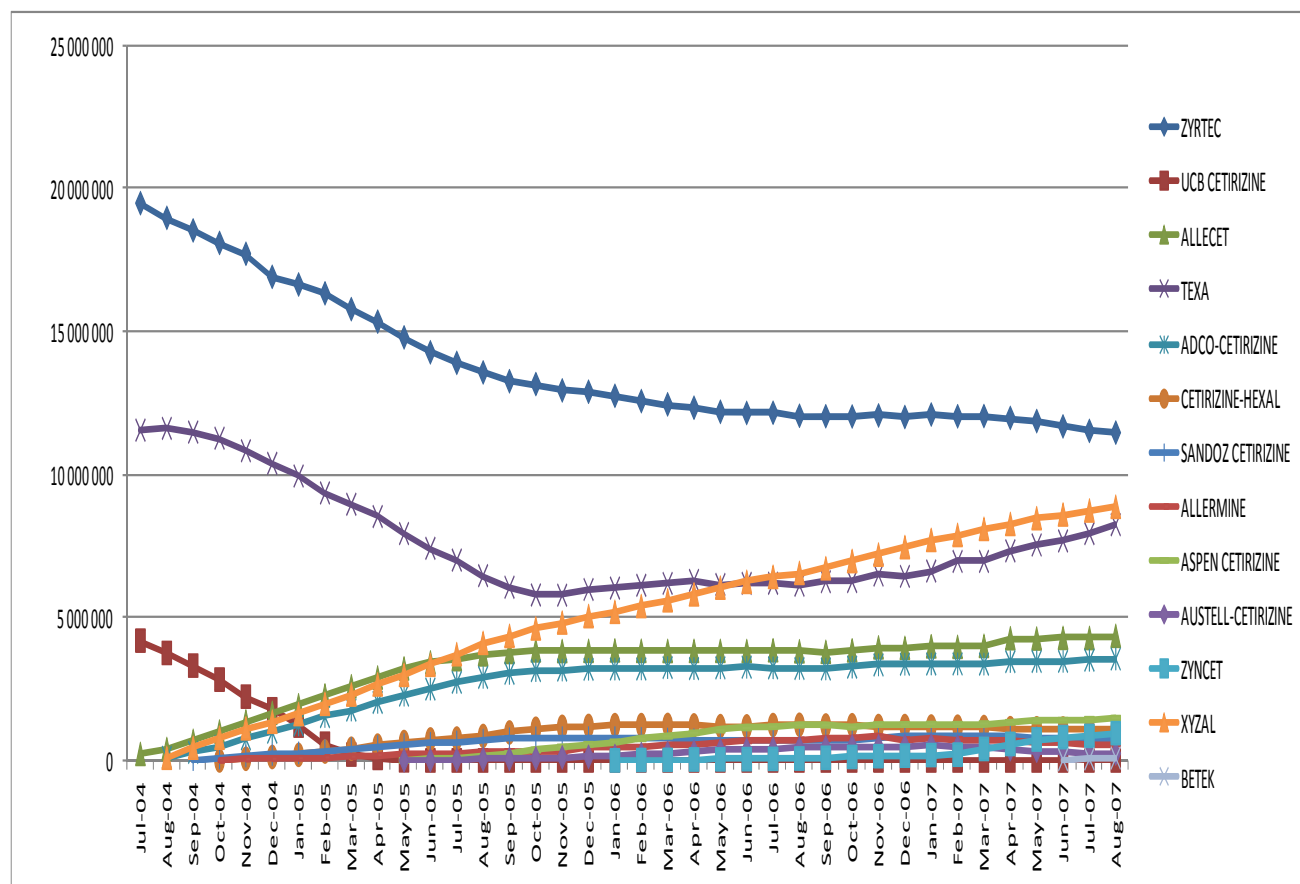


Figure 22: Impact of levocetirizine (XYZAL®) on rand sales in cetirizine market

7.3.2 Impact of Levocetirizine on Market Share

The patent for the original racemate cetirizine (ZYRTEC®) manufactured by UCB had already expired some time before the launch of its single enantiomer, levocetirizine from the same innovator company. Cipla clearly led the cetirizine market with 70% of the total unit sales and 65% of total rand sales.

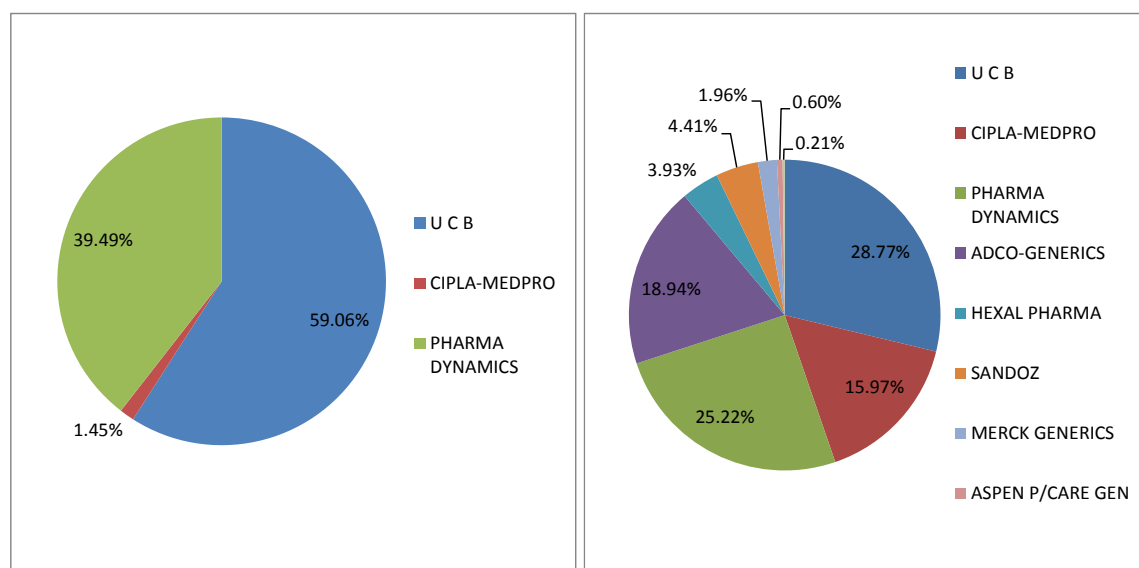
The entry of levocetirizine managed to boost UCB's market share in rand sales but not in the amount of units sold at the end of its first year of launch.

The market share was distributed amongst the many generics that were launched during the second year after the launch of XYZAL®, more evident in the unit sales

than the rand sales. UCB still had the majority of the market with 46% of the total rand sales.

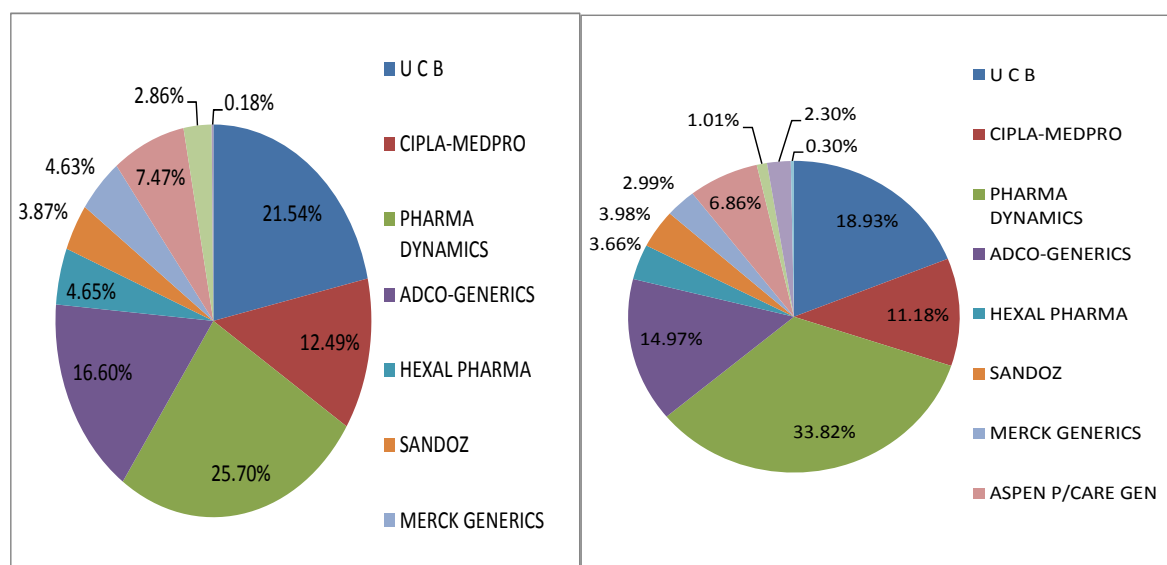
At the end of the third year of this study, Pharmadynamics had sold 325 841 units of TEXA[®], giving it a 31% market share in terms of units sold but, due to its pricing strategy, only had 17% of the market in terms of rand sales. The sale of its single enantiomer medicine allowed UCB to keep the majority of the market share with 43% of rand sales for the market.

Unit sales



(a) Company market share (unit sales) one year before the launch of levocetirizine – September 2003 to August 2004

(b) Company market share (unit sales) one year after the launch of levocetirizine – September 2004 to August 2005



(c) Company market share (unit sales) two years after the launch of levocetirizine – September 2005 to August 2006

(d) Company market share (unit sales) three years after the launch of levocetirizine – September 2006 to August 2007

Figure 23: Impact of levocetirizine on market share (Unit sales)

Rand sales

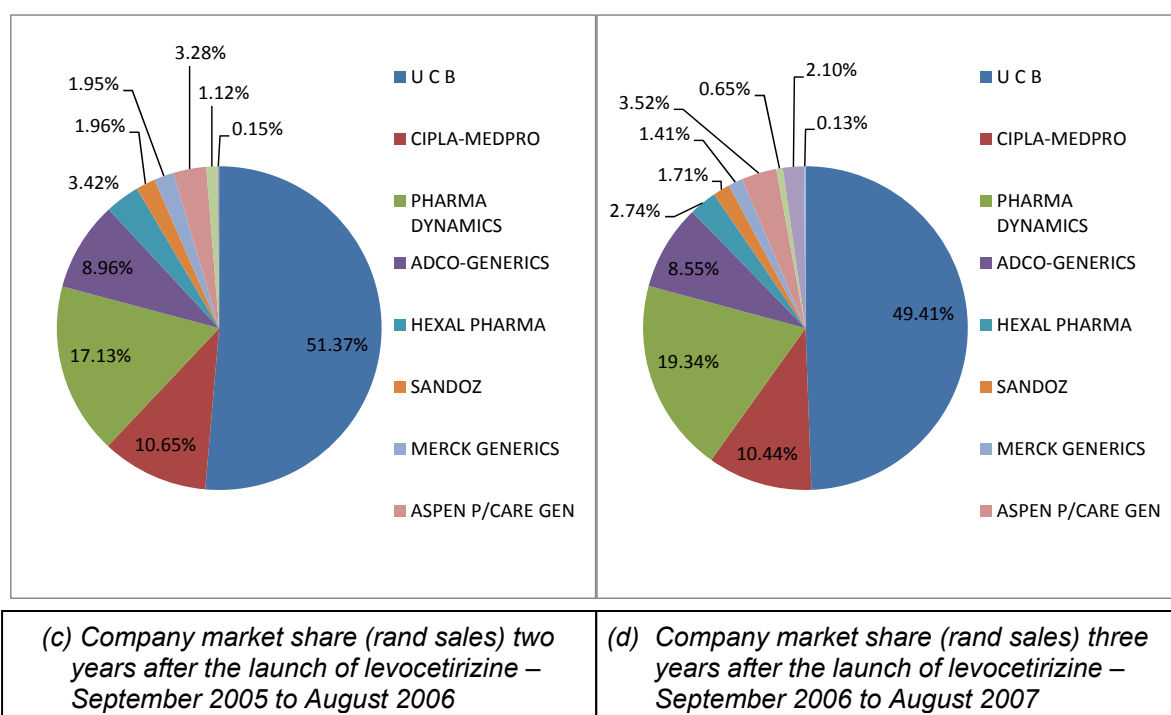
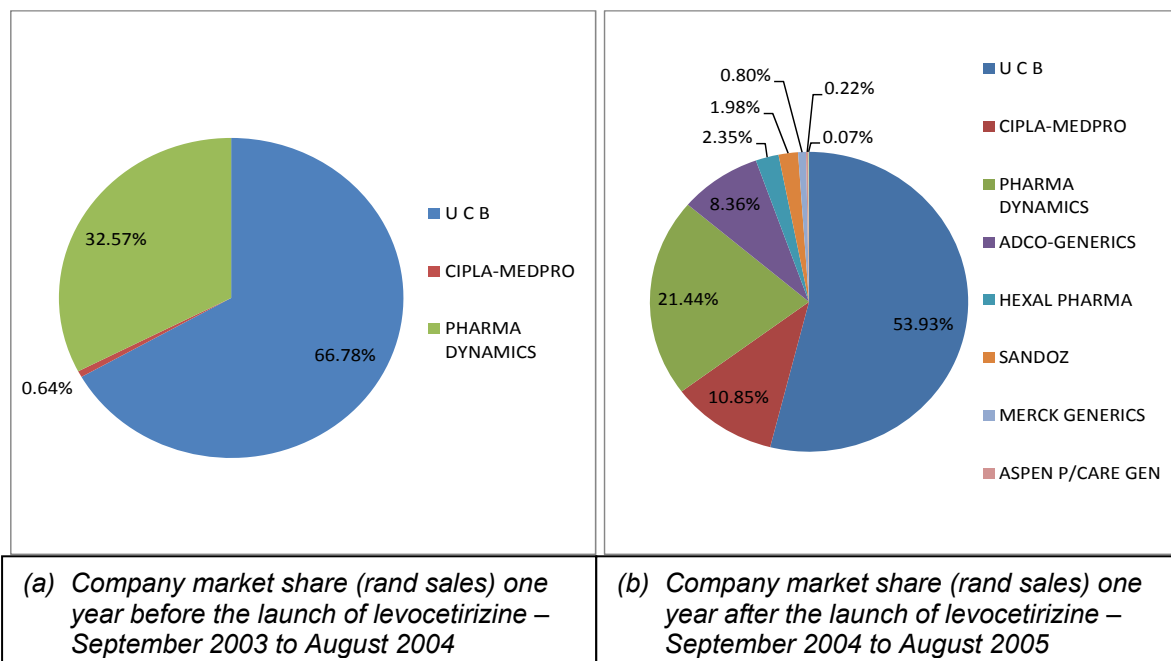


Figure 24: Impact of levocetirizine on market share (Rand sales)

7.3.3 Impact of Levocetirizine on Existing Racemates.

The launch of the single enantiomer, XYZAL[®] did not have a substantial effect on the unit sales of the four racemates that were available on the market – ZYRTEC[®], UCB CETIRIZINE[®], ALLECET[®], and TEXA[®] (represented in Figure 25 and 26). The median increased slightly, and the maximum rose to a large extent during the study period.

The rand sales median decreased a year after the single enantiomer was introduced on the market but then picked up in the following years, although the maximum rand sales did show a decline each year.

Unit Sales

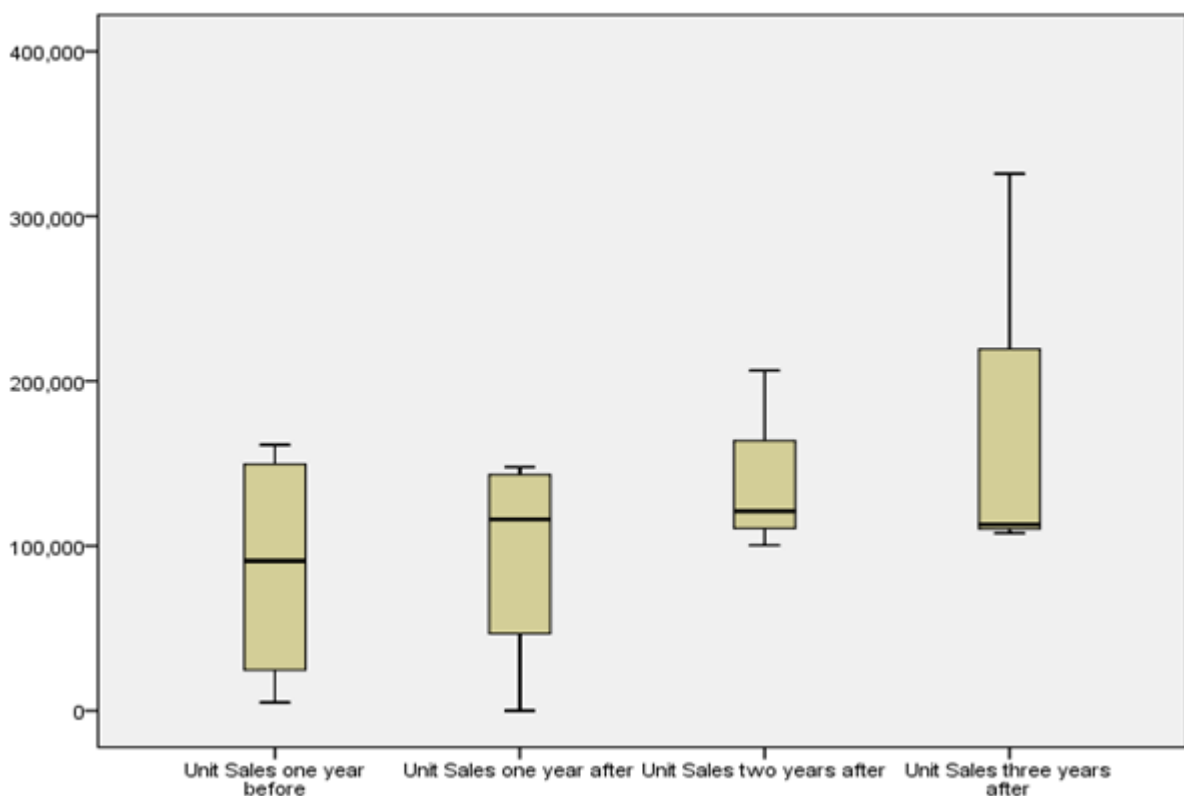


Figure 25: Impact of levocetirizine on existing racemates (Unit sales)

Rand Sales

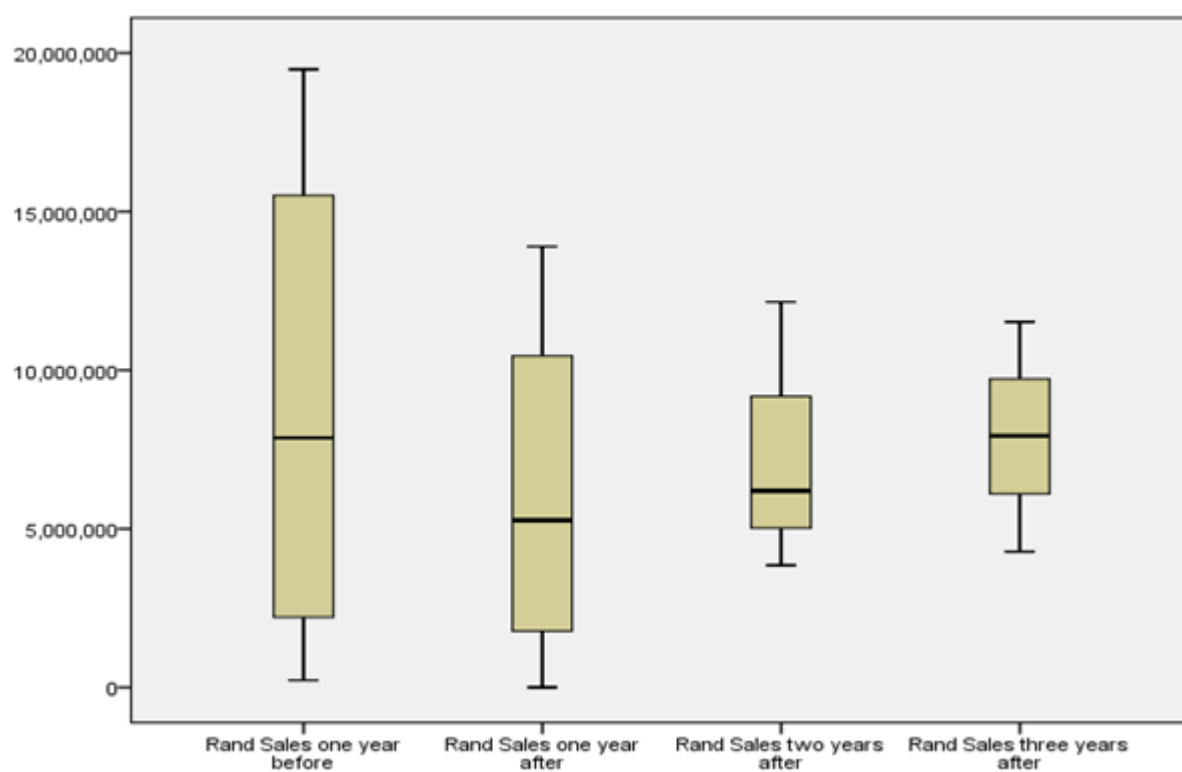


Figure 26: Impact of levocetirizine on existing racemates (Rand sales)

7.3.4 Probability of Levocetirizine being Prescribed or Sold after Launch Compared to Total Cetirizine/ Levocetirizine Market

The probability of XYZAL[®], the single enantiomer, being sold to patients increased by 1.4% between the first and second years and then slightly again by 0.7% between the second and third years post-launch.

Table 6: Probability of levocetirizine being prescribed or sold after launch compared to total cetirizine/ levocetirizine market

Probability of SE prescribed year after launch	Probability of SE prescribed two years after launch	Probability of SE prescribed three years after launch
5.1%	6.5%	7.2%

See Appendix 2 for more details

8. DISCUSSION

In the case of both the prescription-only esomeprazole and escitalopram molecules entering the market, an increase in utilization of the single enantiomer compared to its generics and original racemate were seen in the trend graphs reflecting unit sales.

The results from the study of esomeprazole showed that there was a clear dominance of esomeprazole in both the number of units sold as well the rand sales in that market in the years following its introduction. “Chiral switching” in this case proved not only to bring a perceived increase in clinical efficacy and safety but also a winning financial strategy for the innovator pharmaceutical company. Agranat *et al* (2002) lists esomeprazole as one of the most successful chiral switches worldwide.

A case study conducted in the Netherlands regarding the switch patterns of omeprazole pre- and post- patent expiry showed that most patients (were switched from omeprazole to esomeprazole post patent expiry compared to pre-patent expiry where patients on omeprazole were primarily switched to pantoprazole. The findings suggest that the increase in switch behaviour could have been attributed to the introduction of esomeprazole on the market and could have occurred irrespective of patent expiry (Klok *et al*, 2006).

Escitalopram’s entry onto the market showed a strong growth in drug utilization. The growth of escitalopram utilization was also reflected in the probability calculations showing an increase in the units of the single enantiomer drug prescribed and sold instead of racemate drugs year on year after its launch. A citalopram generic, however, still continued to lead as the prescribed drug of choice during the study period. The escitalopram molecule overtook the citalopram generic in rand sales due to its higher price.

These results show that there could have been a perception of escitalopram being more beneficial than the racemate, citalopram, as there was a steady increase of prescriptions in favour of CIPRALEX[®] dispensed – but perhaps not as convincing to lead the market in terms of units sold. The strategy from a business focus definitely worked in Lundbeck’s favour, although cannibalising its own originator racemate, CIPRAMIL[®], to a certain extent - there was an increase in market share in both unit sales and rand sales for the company due to sales of both the racemate and its single enantiomer products.

The secondary analysis looking at the effect on drug utilization and rand sales once the generics of the single enantiomer, escitalopram, were launched onto the market shows how the generic surpassed the original single enantiomer in both drug utilization and rand sales.

In general, generics make up the vast majority of usage in South Africa - almost 60% of medicines consumed in the private sector are generics (Ribbink, 2011).

A major contributing factor to this statistic could be that pharmacists in South Africa are obligated by legislation to offer generic substitution to a patient in order to make healthcare as affordable as possible. In addition, many medical schemes enforce generic usage, where possible, through the use of formularies or benefit design with the member having to pay a co-payment if they wish to use the originator product. CIPRALEX[®] could have either been prescribed less by doctors in comparison to LEXAMIL[®], or substituted for the generic version at the pharmacy level.

One of the key factors that can explain this result is the difference in price between the molecules. LEXAMIL was launched onto the market at a price of R118.860 for a pack of thirty 20 mg F. C (film coated) tablets in comparison to CIPRALEX[®]'s R366.140 for a pack of twenty eight 20 mg F.C (film coated) tablets.

A recent study conducted by Kaplan *et al* (2013) analysed the relationship between market share volumes of generic and innovator medicines of 19 low to middle income countries from 2001 to 2011. Out of nine countries that were selected for analysis, South Africa was found to have the largest number of Top 30 medicines – which included citalopram and omeprazole- where the increase in the generic market share of the medicine was greater than the decrease in market share of the innovator.

The secondary analysis also highlights the importance of patent protection for the innovator company and the impact a “first-to market” generic can make to its sales and profits. Hollis (2002) evaluated the effect of the timing of generic entry had on ethical drug sales in Canada over a four year period – the results showed that the first generic to be marketed usually had an enduring competitive advantage, gaining approximately 30% of market share. The author, after interviewing several pharmacists, attributed this to a ‘switching cost’ for both the pharmacist and patient. Patients are reluctant to switch to yet another generic due to their lack of knowledge

on bio-equivalence. Pharmacists have little incentive to switch patients as there is not much perceived difference across generics and often times the dispensing fee remains the same. Pharmacies usually stock only one or two brands of generics in order to reduce inventory costs.

The aggressive stance taken by generic companies to gain market share from innovator companies is also apparent in this case study. Similar results could very well be seen within the omeprazole/ esomeprazole market when the impending NEXIAM[®] brand reaches patent expiration.

Marketing of prescription drugs is a complex interaction between pharmaceutical companies, prescribers, patients, regulators and third-party payers with most marketing efforts directed at health professionals in the form of “detailing” visits by sales representatives and print advertising in medical journals. In contrast, OTC medicines are less dependent on the role of the prescriber and direct-to-consumer advertising is allowed. OTC products are generally considered to be “experience” rather than “search” goods and as such there is strong brand loyalty. If a consumer experiences benefits from a particular medicine (idiosyncratic reaction), they are usually reluctant to try any other alternative medicine (risk aversion). Consumers will also have imperfect information as they are usually less informed than health professionals about its efficacy and appropriate uses of other OTC products. Risk aversion and imperfect information can lead to high switching costs and confer important roles such as quality on brand names (Ling *et al*, 2002).

Antihistamines such as cetirizine and other OTC medications are generally not funded by medical schemes and so they are paid out of pocket by the patient who may be more price-sensitive.

These influences could have been responsible for the distinct difference in the results of the cetirizine-levocetirizine market compared to the prescription only case studies.

If there is an established innovator brand favoured by consumers or pharmacists, generic companies have to drop their price margins substantially in order to gain market share, as is evidenced by the results observed in the case of Aspen’s TEXA[®]. TEXA[®], a cetirizine generic, managed to lead the market slightly in terms of volume of units sold due to its pricing strategy. The results of volume of units sold

demonstrate that although there was growth observed for XYZAL[®], there was no significant change to the consumer's or pharmacist's perception of increased clinical efficacy of the single enantiomer – or, perhaps, the low price of the cetirizine generics was more of a deciding factor when choosing in favour of cetirizine over levocetirizine.

UCB, the innovator company, manufacturing both ZYRTEC[®] (cetirizine) and XYZAL[®] (levocetirizine) managed to increase its market share in rand sales demonstrating once again that the “chiral-switching” strategy utilized here also proved successful for the innovator company.

9. CONCLUSION

The results, are consistent with the literature (Hutt and Valentova, 2003; Agranat *et al*, 2002; Tucker, 2000) that deems “chiral switching” to be a successful strategy that allows the innovator company to retain the majority of the market share in its drug class and extend the lifecycle of the product.

The three case studies showed that single enantiomer molecules of an already marketed racemic pharmaceutical product did make an impact on drug utilization, generally showing an upward trend following its launch, indicating that there is a perceived belief of enhanced clinical outcomes for the patient, albeit to differing degrees.

There are, however, many influencing factors specific to each market that make it difficult to draw a general conclusion from the case studies.

The South African pharmaceutical market is a dynamic field in which pricing strategies, prescription status, marketing efforts to physicians and/or consumers and patent challenges make each case study unique.

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APPENDIX 1

	MNF (MANUFACTURER)	LDATE (LAUNCH DATE)	UN MTH/5/03 (VOLUME OF UNITS SOLD MONTHLY)	R MTH/5/03 (RAND VALUE OF SALES MONTHLY)	R/HP MTH/5/03 (PRICE PER PACK)
N6A4 SSRI ANTIDEPRESSANTS (DRUG CLASS)			30 616	7 165 675	234.05
CITALOPRAM (NAME OF MOLECULE)			30 616	7 165 675	234.05
ASPEN P/CARE GEN (COMPANY)			0	0	0.00
CILIFT (NAME OF BRAND)	A&G	5/2003	0	0	0.00
TABS 20MG 30 (DOSAGE FORM, STRENGTH & PACK SIZE)			0	0	0.00
LUNDBECK			30 616	7 165 675	234.05
CIPRAMIL	LUN	9/1994	30 616	7 165 675	234.05
TABS 20MG 28			30 616	7 165 675	234.05
ADCO-GENERICS			0	0	0.00
ADCO-TALOMIL	AOJ	3/2004	0	0	0.00
TABS 20MG 30			0	0	0.00
CIPLA-MEDPRO			0	0	0.00
DEPRAMIL	CD8	4/2005	0	0	0.00
TABS 20MG 30			0	0	0.00
TABS 40MG 30			0	0	0.00
HEXAL PHARMA			0	0	0.00
CITALOHEXAL	HEX	4/2005	0	0	0.00
TABS 20MG 30			0	0	0.00
MERCK GENERICS			0	0	0.00
MERCK-CITALOPRAM	M/G	4/2006	0	0	0.00
TABS 20MG 30			0	0	0.00
RANBAXY			0	0	0.00
RAN-CITALOPRAM	RBV	9/2005	0	0	0.00
TABS 20MG 28			0	0	0.00
TABS 40MG 28			0	0	0.00
SANDOZ			0	0	0.00
SANDOZ CITALOPRAM	SDZ	8/2005	0	0	0.00
TABS 20MG 30			0	0	0.00
TABS 40MG 30			0	0	0.00
ESCITALOPRAM			0	0	0.00
LUNDBECK			0	0	0.00
CIPRALEX	LUN	6/2004	0	0	0.00
TABS 10MG 28			0	0	0.00

APPENDIX 2

APPENDIX 2

Probability calculations

Esomeprazole:

$$\frac{\text{Units of single enantiomer sold year after launch}}{\text{Total units of SE + Racemates sold year after launch}}$$

$$= \frac{148\,531}{428\,716}$$

$$= 0.346 \text{ or } 34.6\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold two years after launch}}{\text{Total units of SE + Racemates sold two years after launch}}$$

$$= \frac{258\,323}{420\,913}$$

$$= 0.614 \text{ or } 61.4\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold three years after launch}}{\text{Total units of SE + Racemates sold three years after launch}}$$

$$= \frac{352\,449}{593\,933}$$

$$= 0.593 \text{ or } 59.3\% \text{ probability}$$

Escitalopram:

$$\frac{\text{Units of single enantiomer sold year after launch}}{\text{Total units of SE + Racemates sold year after launch}}$$

$$= \frac{192\,205}{804\,132}$$

$$= 0.239 \text{ or } 23.9\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold two years after launch}}{\text{Total units of SE + Racemates sold two years after launch}}$$

$$= \frac{385\,613}{1\,066\,448}$$

$$= 0.362 \text{ or } 36.2\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold three years after launch}}{\text{Total units of SE + Racemates sold three years after launch}}$$

$$= \frac{504\,834}{1\,359\,712}$$

$$= 0.371 \text{ or } 37.1\% \text{ probability}$$

Levocetirizine:

$$\frac{\text{Units of single enantiomer sold year after launch}}{\text{Total units of SE + Racemates sold year after launch}}$$

$$= \frac{30\,022}{586\,212}$$

$$= 0.051 \text{ or } 5.1\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold two years after launch}}{\text{Total units of SE + Racemates sold two years after launch}}$$

$$= \frac{51\,865}{803\,091}$$

$$= 0.065 \text{ or } 6.5\% \text{ probability}$$

$$\frac{\text{Units of single enantiomer sold three years after launch}}{\text{Total units of SE + Racemates sold three years after launch}}$$

$$= \frac{69\,458}{963\,529}$$

$$= 0.072 \text{ or } 7.2\% \text{ probability}$$