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A RETROSPECTIVE ANALYSIS OF THE GROWTH OF NON GENERISIZED PROTON PUMP INHIBITORS AFTER THE LAUNCH OF GENERIC MOLECULES IN THE SAME THERAPEUTIC CLASS

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Science in Pharmaceutical Affairs.

Johannesburg, October 2006.

Declaration

I, Ajit Madhav Mangalmurti declare that this research report is my own work. It is being submitted for the degree of Master of Science in Pharmaceutical Affairs in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature ……..

October 2006

Abstract

Background

The South African Healthcare landscape has changed dramatically over the last two years with the implementation of mandatory substitution, single exit pricing and prescribed minimum benefits. The private market for medicines is becoming more competitive and commoditized. Between July 2004 and June 2005 there were 119 generic registrations at the Medicines Control Council. In the US and Canada research has been conducted on the change in prescribing behaviour induced through incentive based formularies and the impact of generic medicines on healthcare costs. This research protocol aims to build on this body of knowledge by analysing sales trends within a therapeutic class after the launch of a generic molecule in the same class. This research investigates how the introduction of generics may impact the growth of the innovator molecules and subsequent generics. The therapeutic class Acid Pump Inhibitors has been selected.

Method

Unit sales of Proton Pump Inhibitors are drawn monthly from sales in the total private market. They are then grouped by molecule and comparisons are drawn between the originator and it's generic to determine association. This is also done at the aggregate level where the originators form one group and generics the second group. Each aggregate group's average growth in the therapeutic class is then calculated to determine the aggregate group's evolution index.

Data Analysis

Data is analysed through descriptive and interpretative statistics. The descriptive statistics establish a relationship between generisized molecules and the non generisized molecules. A t-test for two independent means is used to test the hypothesis that the non generisized molecules in the therapeutic class have a significant higher growth.

Conclusion

The results demonstrate that the number of units sold of the generisized molecules increase as they become more affordable, however contrary to intuition the number of

units sold of the non generisized molecules also increase. The research shows that there is a statistically significant greater growth, albeit on a smaller base, of the non generisized molecules over generisized molecules.

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Abbreviations

IMS	Internal medical sales
MAT	Moving annual totals
EI	Evolution index
MCC	Medicines Control Council
PPI	Proton pump inhibitors
SEP	Single exit pricing
API	Active pharmaceutical ingredient

Glossary

The Act:

Medicines and related substances control Act 101 of 1965 as amended.

Active pharmaceutical ingredient (API):

Is a substance or mixture of substances intended to be used in the manufacture of a medicine and that becomes an active ingredient of the medicine. API's are intended to cause pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or function of the body.

Aggregate data:

When referring to aggregate data it is implied that the data is not molecule specific. Data is grouped into two broad aggregates, generisized molecules and non generisized molecules.

Dispensing fee

Is the amount, which is as yet to be decided by MCC, that will be deemed to be an appropriate dispensing fee to be charged by a pharmacist or by a person licensed in terms of section 22C (1) (a) of the Act as remuneration for dispensing a medicine.

Evolution index (EI):

The Evolution index for a product is a statistic calculated by Internal Medical Sales (IMS) per local market. It is used internationally as a measure of growth of a product in relation to the growth of the class to which the product belongs.

Product growth for territory = x%
Therapeutic class growth for the territory = y%

(100 + x%) / (100 + y%) % = EI%

EI indicates that your product is performing better (>100) or worse (<100) than the therapeutic class as a whole.

First to market generics:

A first to market generic is a molecule that is approved and registered for sale by the relevant medicines regulatory authority of a country once the patent on the originator molecule has expired.

Generics:

Generics or interchangeable multi-source medicines means medicines that contain 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 in the regulations to the Act.

Internal Medical Sales (IMS):

Internal Medical Sales Health is an organization that collates and compiles sales and product data related to sales across four areas, namely, dispensing doctors, private hospitals, non-retail pharmacy outlets and retail pharmacy outlets.

Logistics fee

Logistic or distribution fee, the amount which is as yet to be decided by the Medicines Control Council (MCC), to be charged by wholesalers or distributors or any other person for the distribution Scheduled medicines.

Mandatory substitution

A pharmacist is obliged in terms of the Act to dispense a generic of a branded medicine unless expressly forbidden by the patient to do so.

A pharmacist shall not sell an interchangeable multi-source medicine-

(a) if the person prescribing the medicine has written in his or her own hand on the prescription the words 'no substitution' next to the item prescribed;

(b) if the retail price of the interchangeable multi-source medicine is higher than that of the prescribed medicine; or

(c) where the product has been declared not substitutable by the Council.

Me-too generics:

Me-too generics are generic medicine that have been launched after the first to market generic medicine and are also approved and registered by the relevant medicines regulatory authority of a country.

Medicines Control Council (MCC):

The Medicines Control Council (MCC) is a statutory body that was established in terms of the Medicines and Related Substances Control Act, 101 of 1965, to oversee the regulation of medicines in South Africa. It is appointed by the Minister of Health and its main purpose is to safeguard and protect the public through ensuring that all medicines that are sold and used in South Africa are safe, therapeutically effective and consistently meet acceptable standards of quality.

Molecule specific data:

Molecule specific data is all the data that is relevant to one molecule e.g. Omeprazole.

Moving Annual Totals (MAT):

Moving annual totals are the totals achieved for a period of twelve months. For every new month added to the total the oldest month is dropped off. This ensures that at any point the total reflects twelve months only. MAT is used to smooth out inter month variations. These variations are attributable to stock in the supply chain.

Originator molecule:

An originator molecule is a molecule that has been developed by an individual or an organization through a process of original research and development. This molecule has to be proven to be efficacious and safe in humans before it can be registered by the relevant medicines regulatory authority of the country and only then can it be taken to market. Safety and efficacy is proven by way of rigorous clinical trials. The cost to develop an originator molecule can be upwards of USD 800m and often takes seven to eight years. Once the molecule is registered it enjoys a period of patent protection.

Prescribed minimum benefits:

Prescribed minimum benefits is a basic benefit package covering twenty five chronic illness on which compulsory medical cover will be provided by medical schemes.

Private market

The private market is defined as the sum total of medicines prescribed to those individuals that are serviced by private hospitals, retail pharmacies, non retail pharmacies and dispensing doctors that do not obtain their stock through a process of government tenders and distribution.

Public market

The public market encompasses all the medicines that are procured by a process of government tenders and prescribed in public hospitals, public clinics and by health practitioners who have obtained stock from the government distribution centers.

Proton pump inhibitors (PPI)

Proton pump inhibitors are a group of drugs whose main action is the pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today. These drugs are among the most widely selling drugs in the world as a result of their outstanding efficacy and safety. Structurally, all of these drugs are substituted benzimidazoles.

Single Exit Pricing (SEP)

The single exit price is the price which is published by the manufacturers and the only price at which a manufacturer can sell medicines and Scheduled substances to any person other than the State. No pharmacist or person licensed in terms of section 22C (1) (a) of the Medicines and Related substances control act 101 of 1965 as amended or wholesaler or distributor can sell a medicine at a price higher than the single exit price.

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1 Introduction

1.1 What is a generic medicine?

A pharmaceutical product derives its efficacy and safety from the chemical active it contains, also known as its active pharmaceutical ingredient (API) [1]. This chemical active or molecule is the result of many years of research and expense. The intellectual property on this molecule is closely guarded and protected by registering various patents on the product. Significant international harmonization of a patent's term across national laws was provided in the 1990s by the implementation of the World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs Agreement). Article 33 of the TRIPs Agreement provided that the term of protection available for patents shall not end before the expiration of a period of twenty years counted from the filing date. This ensures that the molecule can be commercialized profitably before attracting competition.

Once the life of this patent, has expired the molecule if still commercially viable may be generisized. Generisized means that the molecule is now manufactured by companies other than the originator without infringing on any patents. To be classed as a generic of the originator the manufacturer of the generic has to prove to the relevant authority that the generic is therapeutically equivalent to the originator.

The requirements for therapeutic equivalence[2] are:

(1) A medicine is considered therapeutically equivalent to another medicine if both medicines:-

- are pharmaceutically equivalent, i.e., contain the same amount of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route; and
- after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same.

(2) Therapeutic equivalence is determined from comparative bioavailability,

pharmacodynamic, clinical or in vitro studies which meet the requirements and accepted criteria for bioequivalence as determined by the Council.

1.2 Market trends of generic medicines in South Africa

The South African medicines market is divided into two exclusive markets, the State and the Private sector. IMS (Internal Medical Sales) is the premium source of sales and market share data in the private market in South Africa. IMS data measures the units and value of stock sold monthly (Annexure 1 - IMS data sheet sample).

The Medicines Control Council (MCC) is the only regulatory body in South Africa that can register a medicine for sale in South Africa. From July 2004 to June 2005, 119 registrations for generic medicines were approved by the Medicines Control Council. This rate of approvals is expected to continue as there are many announcements of new registrations on the MCC website (www.mccza.com). The launch of a generic medicine creates competition and reduces the cost of a particular molecule.

While intuitively one would suspect that the introduction of new generics, single exit pricing (SEP) and mandatory substitution would reduce the cost of medicines, Rand sales data on the total private market (IMS) suggests that market expenditure on medicines has grown by 10%[3] from 2005 to 2006. This could possibly be explained by the implementation of prescribed minimum benefits[4] whereby the healthcare insurer is now compelled to provide cover for 270 conditions which are treated in hospital as well as 25 chronic diseases and hence provides more medicines cover. However, spending in the insured market on pharmaceuticals has decreased from R8.7b in 2003 to R8b in 2004[4].

These are conflicting trends, whereby legislation is moving towards making medicines more affordable, but spend on medicines in the private market is on the increase taking into account a population increase. The other conflicting trend

is that more chronic conditions are now reimbursed but spend on medicines by the medical schemes has decreased.

This makes the interpretation of market trends in the South African generic market more challenging. One trend that the investing community generally agrees on is that the growth of generics is estimated at 27% per annum till 2009[5].

1.3 South African medical schemes data on pharmaceutical spend

South Africa's demographics can be constructed as a three layered pyramid. With the top layer comprising of 7 million privately insured lives, the private market. A middle layer of 14 million lives comprising of employed but uninsured individuals, the emerging market. The bottom layer comprising of 24 million lives of unemployed or informally employed and uninsured individuals that avail exclusively of public healthcare.

Data presented in the Medical Schemes Council Annual Report 2004, the private market, states that monies spent on pharmaceuticals through medical scheme reimbursements has decreased from R8.7b to R8b while the number of members has remained constant on 7million.

Insurance coverage for drugs reduces the sensitivity of the consumer to price differences and enhances the ability of pharmaceutical companies to set their prices well above the cost of production and distribution[6]. Healthcare payers have several mechanisms to implement price controls. These are capping of prices of new drugs, reference pricing drugs to same drugs in other similar countries, item by item pricing that takes into account degree of innovation in country of origin, imposing capitated reimbursement schemes to providers, rate of return profit regulations and reference pricing lists.

It appears from medical scheme reference pricing lists[7], that the manufacturer's list price has remained static from 2003 to 2006 and reimbursement of medicines is set at list price plus a dispensing fee. The Department of Health had put a moratorium on price increases for the last three years.

Medical schemes data has been relatively static in terms of pharmaceutical price and spend[4] between 2004 and 2005. Therefore, the impact by medical schemes on the growth of medicines in the private market through pricing pressure and number of members has been limited.

1.4 Change in spending patterns on generic medicines in South Africa

Generics accounted for almost 50% of the market in volume and for a third of sales value[5] in 2005 this is up from 30% of the market in volume and 20% of sales value in 2004.

Pre SEP, which was implemented on 1 August 2004, the dispensing of a particular brand of generic medicine was largely determined by the margin a retailer would make as long as it was approved by the MCC. Prior to mandatory substitution the retailer could dispense the branded product even if there were much cheaper generic versions of the medicines available.

Post SEP the incentive to prescribe a particular brand of a generic is no longer determined by the margin a retailer can make. Following mandatory substitution the justification to prescribe a branded medicine when there is a generic available has become much more onerous.

What this has led to is the tightening of what is reimbursed and at what level by the medical schemes. Medical schemes now have a legal justification to approve only the cheaper generic and at the same time to substitute away from the more expensive branded product.

Therefore, it appears that although private market sales are increasing by 10% it is not through more monies being spent by medical schemes but by the individual out of his or her pocket.

This “out of pocket expenditure” phenomenon may be created when the funds

available to an individual from a medical scheme are not able to meet the expenditure on medicines. Alternatively, the medicines that are being prescribed are either partially or wholly not covered by the medical scheme. This would imply that, in the context of generic medication, only generic medicines are approved by the medical scheme and non generics are allocated to the member's personal account.

This raises the question as to whether a non generic would ever be prescribed over a generisized molecule. The Medicines and Related Substances Control Act 101 of 1965 (The Act) as amended[8] makes provision for the prescription of a non generic under certain conditions. These conditions include that the doctor prescribing a generisized medicine has to hand write on the script that the medicine is not substitutable. Depending on medical scheme rules the scheme then may either reimburse the patient or ask the patient to pay the difference between the cost of the branded medicine and the generic medicine.

A study of IMS data, however, shows that originator products are still prescribed. They decline in sales sharply once a generic is launched, though they do not disappear completely. Therefore, there is still a market for the originator medicine even if it is generisized, even though the originator molecule may have a statistically insignificant different efficacy or safety profile to the generic molecule as a result of the way its API was synthesized. Alternatively, the "branded" product may be perceived as the "gold standard" although this may be difficult to justify scientifically.

The change of spending patterns has two dimensions. Firstly there has been a change towards generics bought about by legislation. Secondly there has been a change in who is spending money in the private market. The Council of Medical Schemes Report 2006 suggests that there was a benefit payout on medicines of Rand 7.2 million in 2005 and a drop of 11.6% (inflation adjusted) between 2002 and 2005. With private market expenditure on medicines growing it appears that the insured individual is now spending more on medication compared to the medical scheme.

1.5 International financial trends of generics

Data from adults included in the American Medical Expenditure Panel Survey 1997-2000 indicates that there would have been a saving of approximately USD 8.8b or 11% if all possible originator drugs would have been substituted with their generic equivalent[9]. The important conclusion from this survey is that generic substitution would only affect a modest percentage of drug expenditure (11%); however, it could result in a substantial absolute saving. In other words the impact of generic substitution would affect a modest proportion of the total drug bill.

One would expect that the introduction of me-too generics would erode the price of the first to market generic. The Canadian experience[10] indicates that first to market generics accounted for 53% of total expenditure and 75% of total use in 1996 and 27% of expenditure and 54% of total use in 2003. On the other hand me-too generics accounted for 63% of expenditure and 44% of use by 2003. The average cost of me-too generic brands per day of treatment was four times that of first to market generics. An interpretation of the above statistics would suggest that initially generics help to bring the price of medicines down. Subsequent generics bring the cost of treatment up again. This result is note worthy as one would believe more generics help to commoditized the market and bring the price of medicines down.

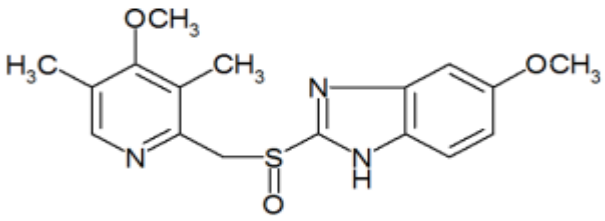
Me-too generics are a profitable business. The first generic has to often defend patent infringement challenges by the manufacturer of the originator and resistance by the doctor and patient. Me-too generics on the other hand enter an established market. Me-too generics can also have higher margins than first to market generics as they can enjoy the benefits of more modern automated manufacturing equipment such as high speed tablet presses, integrated processes such as integrated fluid bed dryers for drying of powders verses oven drying and the commoditization of the active pharmaceutical ingredient often from low cost countries like India and China contributing with world class API synthesis which

was historically the domain of costlier first world European manufacturers.

Therefore, most trends point to an increase in the use of generic molecules. This research report questions this intuitive reasoning by investigating a particular therapeutic class of drugs. The therapeutic class chosen is the proton pump inhibitors.

1.6 Proton pump inhibitors

1.6.1 Structure



1.6.2 Clinical Use

Schedule 2 and 4 medicines in terms of the Medicines Control Act No. 101 of 1965.

These drugs are utilized in the treatment of many conditions such as[11]:

- dyspepsia
- peptic ulcer disease (PUD)
- Zollinger-Ellison syndrome
- Gastroesophageal reflux disease (GORD/GERD)
- Prevention of stress gastritis
- Gastrinomas and other conditions that cause hypersecretion of acid

1.6.3 Mechanism of action

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system[11] (the H^+/K^+ ATPase, or more commonly the gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. Targeting the terminal-step in acid production, as well as the irreversible nature of the inhibition, result in a class of drugs that is significantly more effective than H_2 antagonists and reduces gastric acid secretion by up to 95%[11].

The lack of the acid in the stomach will aid in the healing of duodenal ulcers, and reduces the pain from indigestion and heartburn, which is caused by excess stomach acid.

The proton pump inhibitors are administered in an inactive form[12]. The inactive form is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

1.6.4 The pharmacokinetics of Proton Pump Inhibitors

Generally, the absorption[12] of proton pump inhibitors is unaffected by co-administration with food. The rate of omeprazole, lansoprazole and esomeprazole absorption is decreased and delayed by food. These pharmacokinetic effects, however, reportedly have no significant impact on efficacy.

The elimination half-life of proton pump inhibitors ranges from 0.5–2 hours,

however, the effect of a single dose on acid secretion usually persists up to 2–3 days. This is because of accumulation of the drug in parietal cell canaliculi and the irreversible nature of proton pump inhibition.

1.6.5 Clinically used proton pump inhibitors:

- Omeprazole (brand names: Losec, Omiloc ,Omez, Sandoz Omeprazole, Adco-Omeprazole, Altosec, Nozer)
- Lansoprazole (brand names: Lanzor, Lanzoloc, Adco-Roznal, Aspen Lanzoprazole)
- Esomeprazole (brand name: Nexium)
- Pantoprazole (brand names: Pantoloc, Controloc, Topozole)
- Rabeprazole (brand name: Pariet)

1.6.6 Adverse effects

Proton pump inhibitors are generally well tolerated, and the incidence of adverse effects[12] is relatively uncommon. The range and occurrence of adverse effects are similar for all of the proton pump inhibitors, though they have been reported more frequently with omeprazole[12]. This may be due to its longer availability and hence clinical experience. Common adverse effects include: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness.

Infrequent adverse effects include: rash, itch, flatulence, constipation. Decreased cyanocobalamin (vitamin B12) absorption may occur with long-term use[12].

Recently it has been observed[13] that gastric acid suppression, using H2-receptor antagonists and proton pump inhibitors, is associated with an increased risk of community-acquired pneumonia. It is suspected that acid suppression results in insufficient elimination of pathogenic organisms. It has, therefore, been suggested[13] that patients at higher risk of pneumonia should only be prescribed proton pump inhibitors at lower doses and only when necessary.

1.7 Reasons why Proton Pump Inhibitors were used in the Research

- The class is well populated with various molecules (5) of which one is an isomer.
- Large multinationals as well as local companies market the molecules in the class.
- The class has a large market value of approximately R320m and market share is well defended by the manufacturers through advertising and promotions.
- There have been numerous generics launched in this class in the time period of the study.
- Therapeutic and generic substitution is prevalent in the class, i.e. there is movement within the class.
- The class is prescribed at both the surgeon and physician level.
- Proton pump inhibitors are prescribed for both acute and chronic conditions.
- Two molecules in the class, namely Pariet and Nexium have no generic equivalents in the time frame of the research which makes for a good comparison of 2004, 2005 and 2006.

1.8 Evolution Index

The rationale for using the evolution index (EI) of a medicine as a means to determine growth was the following:

- Growth in the population does not affect the evolution index as it is based on a rate of growth.
- It is a mathematical way to determine if the medicine is growing at a faster rate or slower rate compared to the rest of the market. Where an EI is 100 the medicine is growing at the same rate as the market i.e. it is not gaining

market share. If an EI is less then 100 then the medicines is losing market share and vice versa.

- The EI of a medicine in a therapeutic class is independent of whether the total market is growing or declining for the therapeutic class in relation to other classes.
- The EI is an independent stochastic variable.

1.9 Limitations of the study

1.9.1 New legislation

One of the confounding variables that might influence this study is the rapid change over the last twenty four months of the South African pharmaceutical landscape. This change has been driven by legislation[8] and the regulations set out by the Council of Medical Schemes[4] to align the healthcare industry with national healthcare policy.

1.9.2 Single exit price

Historically medicines were marked up by 50% off the manufacturer's list price. The profit a retailer would make would be the difference between a discount or rebate off a manufacturer's list price and the marked up price. As competition increased retailers started discounting this markup. With the advent of SEP, manufacturers stopped rebates and discounts on the list price and the retailer's markup was replaced by a dispensing fee.

The introduction of the single exit price has had a significant impact. Single exit price is the drug price that pharmaceutical companies set and what the retailer has to charge by law. It cannot be influenced by bonusing, rebates and discounts. The strategy was designed to have saved between 50%-70% of drug

related costs; however, in reality the figure is closer to 14%.

1.9.3 Dispensing fee

The mechanism of the as yet not finalized dispensing fee being charged by pharmacists is based on a flat fee for medicines. As per the current Department of Health legislation, where SEP is less than or equal to R100, 26% of the SEP is added to the price of the medicine as a dispensing fee. For medicines with an SEP greater then R100, a flat dispensing fee of R26 is charged. The incentive to prescribe more expensive medication is therefore still there as prescribing a medicine greater then R100 guarantees the R26 dispensing fee.

1.9.4 Logistics fee

The logistic fee which is as yet also undecided has put the future of wholesalers into uncertainty as they are unsure whether they will have viable businesses if this fee is set too low. However, at this point the logistics fee could be used as a mechanism by retailers to extract discounts from manufacturers to promote a particular brand of medicine. Retailers could hide discounts received as a logistics fee paid to a distributor with whom they have an affiliation.

1.9.5 Reimbursement of generic medicines

Another factor that may have influenced the price of generics is that insurance coverage for generic drugs is set at 100% of the SEP which ensures that reimbursements rates for drugs can be set well above the cost of production and distribution[6]. This results in the desensitization of the individual to the price of the generic drug. The individual's concern now only extends to whether the medicine fully reimbursed by the medical scheme and not to any value for money concept.

1.9.6 Other variables

Other confounding variables such as changed adherence to medication [14, 15] and formularies [16, 17] are not dealt with in this report.

2 Aims and objectives of the research

2.1 Statement of the problem

The launch of a generic molecule in a therapeutic class results in the originator molecule loosing market share as cheaper versions of the molecule become available. Medical schemes and legislation oblige doctors and pharmacists to prescribe away from these generisized originator molecules to the cheaper generics. This report considers the sales impact on the non generisized molecules when a generic is launched in the same therapeutic class.

2.2 Aim

This research compares the unit growth as measured by the evolution index of generisized and non generisized molecules in a therapeutic class as more generics are launched in the class. It analyses whether the launch of generics leads to a significant unit growth of non generic molecules in the same therapeutic class.

2.3 Objectives

1) Collect moving annual totals (MAT) data on PPI between August 2003 and May 2006 (34 months) to determine the trends in sales volume between the various PPI.

2) Calculate the evolution index (EI) of the various molecules of the therapeutic class to determine growth of each product in the therapeutic

class.

3) Plot the trends in EI between the generisized molecules and non generisized molecules to determine whether generic substitution may be prevalent.

4) Group EI's into two categories namely generisized molecules and non generisized molecules in the therapeutic class proton pump inhibitors so as to be able to compare the EI's of the two groups.

5) Calculate the average EI per month of each group so as to be able to compare the average EI of the two groups by means of a t –test to determine if the average growth of products in one group is significantly different from the average growth of products in the other group.

6) To interpret the result obtained in objective 5 with reference to market trends, medical scheme data, spending patterns and legislation.

3 Methodology

A list of generic and originator products was identified for the PPI class. These included the following molecules; Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole and Esomeprazole (S-isomer of Omeprazole).

Each molecule had an originator. At different stages in the study time period, sales data on one or more generics of the molecule appeared and this data extended to the end of the study period. There were only two exceptions to this:

- Ulsec – Ulsec was taken off the market as it had infringed on the originator Losec's patent.
- Controloc and Pantoloc – These are identical originator molecules but branded differently.

There were no generics of Rabeprazole and Esomeprazole launched during the period of this study.

3.1 A review of launch dates and categorization into molecule class

1) The Medicines Control Council (MCC) website was reviewed to obtain all Proton Pump Inhibitors (PPI) launched in the last 6 years.
2) A list of all expired patents from the patents office (Annexure 2) was obtained.
3) All new PPI launched in the last 34 months, specifically August 2003 to May 2006 were extracted from IMS. This extract contained the name of the product, the date it was launched and the number of months it has been in the market (Annexure 3).
4) The study began with 5 products in August 2003 and the analysis finished in May 2006 with 18 products under review.
5) A comparison on launch dates and registrations was done on the information found on the MCC web site, IMS and the patent office to determine the exact date when an originator or generic should appear on the data sheet, Annexure 6.
6) All PPI launched were categorized into an appropriate molecule class, see table 1.

Table 1 PPIs categorized per molecule

	Molecules				
	Omeprazol	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
Products	ULZEC	LANZOR	PANTOLOC	PARIET	NEXIAM
	LOSEC	LANZOR HB	CONTROLOC		
	OMEZ	ADCO-ROZNAL	TOPZOLE		
	SANDOZ OMEPRAZOLE	LANSOLOC			
	ADCO-OMEPRAZOLE	ASPEN-LANSOPRAZOLE			
	ALTOSEC				
	OMILOC				
	NOZER				
	LOSEC MUPS				

3.2 Extraction of unit sales data on proton pump inhibitors

Retrospective Internal Medical Sales (IMS) data on proton pump inhibitors was collected by reviewing and capturing sales data per month over a period of thirty four months, from August 2003 to May 2006. The unit sales data used was the moving annual totals (MAT) for each product (Annexure 6).

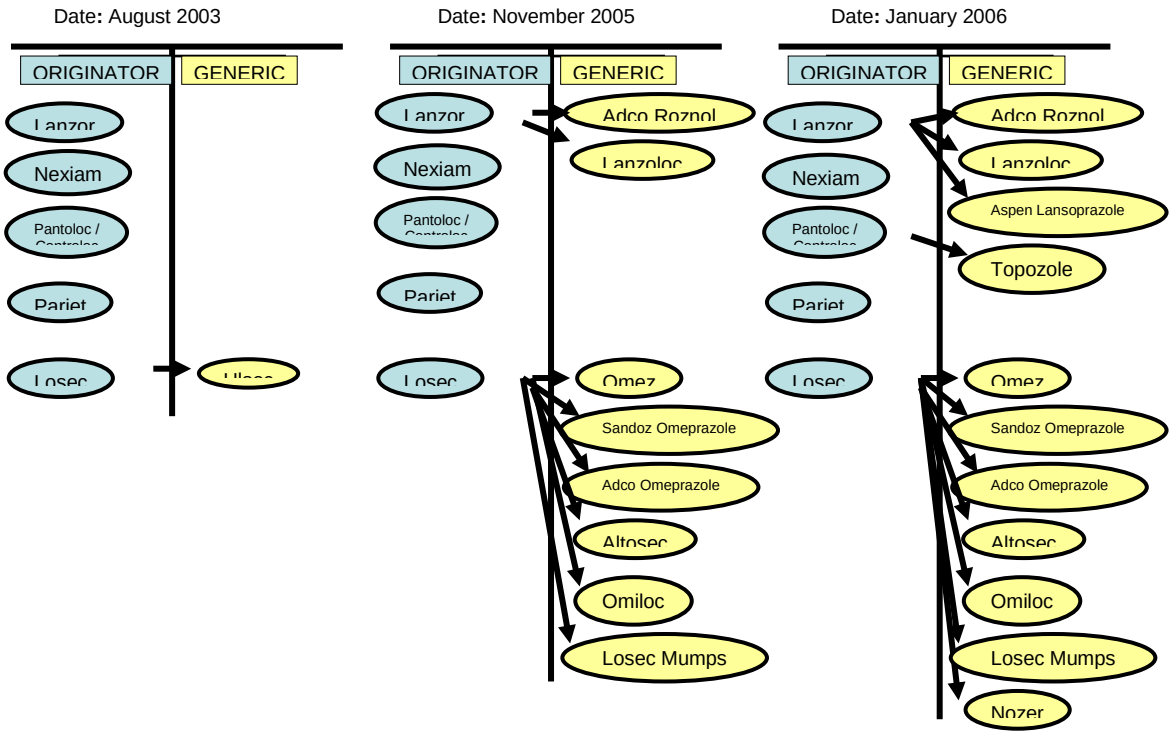
Sales data was numerical and did not need to be formatted. The MAT unit sales data was tabulated into an electronic file for ease of manipulation. The reason MAT was used instead of monthly unit sales was to reduce the impact of monthly variations in sales data.

3.3 Allocation of each Proton Pump Inhibitor into either the generisized or non generisized group

1) PPI were sorted by using the date of launch as the primary key in ascending order. This assisted in determining the originator and the generic/s.
2) Each PPI was allocated to a group at the start of the study period.

3) At the point where a generic of the originator molecule was introduced, the originator molecule was moved into the generisized group (Figure 1).

Figure 1 Maturation of originator molecules by date order



3.4 Calculation of average evolution per grouping

Once the product had been allocated to a grouping, the average evolution per month in each group was calculated over the thirty four months. This average was the simple average of all the EI's in the group for the month. Only if a product appeared for the month in the group would it be used in the calculations. The group average per month was entered below the last product in the group (Annexure 7).

4 Data Analysis

Data Analysis was divided into three parts.

4.1 Descriptive Statistics

(1) Scatter plots were created with moving annual totals (MAT) units of the therapeutic class less the generisized molecule on the Y axis and the generisized molecule on the X axis at the aggregate level and the molecule specific level. Data was plotted for thirty four months and lines of best fit were drawn through the data (see also Figures 2 to 12). A combined graph to determine if there was any correlation between the various molecules in the class was also drawn (see Figure 4).

(2) Separate graphs of the evolution index of the generic molecule and the remainder of the therapeutic class were plotted. Polynomial lines of best fit were drawn through this data.

(3) The mean growth and variance of the generisized molecule and the remainder of the therapeutic class was calculated.

4.2 Measuring Association

Pearson's correlation coefficient was used to determine correlation and the coefficient of determination was calculated to determine goodness of fit for Figures 2,5,7,9 and 12 (See Annexure 6 and 7).

4.3 Statistical Inference: Hypothesis Testing

Hypothesis

The launch of generic proton pump inhibitors in South Africa has no effect on growth of non generic molecules in the same therapeutic class. The alternate hypothesis is, that the launch of generics, either increases or decreases growth.

The following t-test for two independent means to test the hypothesis was used where:

1. Ho: $\mu_1 = \mu_2$; H_1: $\mu_1 \neq \mu_2$
2. $\alpha = 0.05$
3. Test statistic:

$$T = \frac{(X_1 - X_2 - (\mu_1 - \mu_2))}{\sqrt{(((n_1-1)S_1^2 + (n_2-1)S_2^2)/(n_1+n_2-2))(1/n_1+1/n_2)}} \sim t(v)$$

n is the population size

S is the sample

X_1 is the mean EI of generisized molecules

X_2 is the mean EI of non generisized molecules

4. Reject H_0 if $t \leq -2.145$ or ≥ 2.145

If the average evolution index of the generisized molecules is significantly greater then the non generisized molecules it would imply that there was a growth in the generisized molecules and there was not as much increase in the use of alternative

drugs in the same therapeutic class.

If, however, there is a statistically significant higher growth in non generisized molecules in the same class then the generisized molecule this would imply that the impact of the launch results in either therapeutic substitutions or growth in molecules other than the generisized molecule.

5 Results

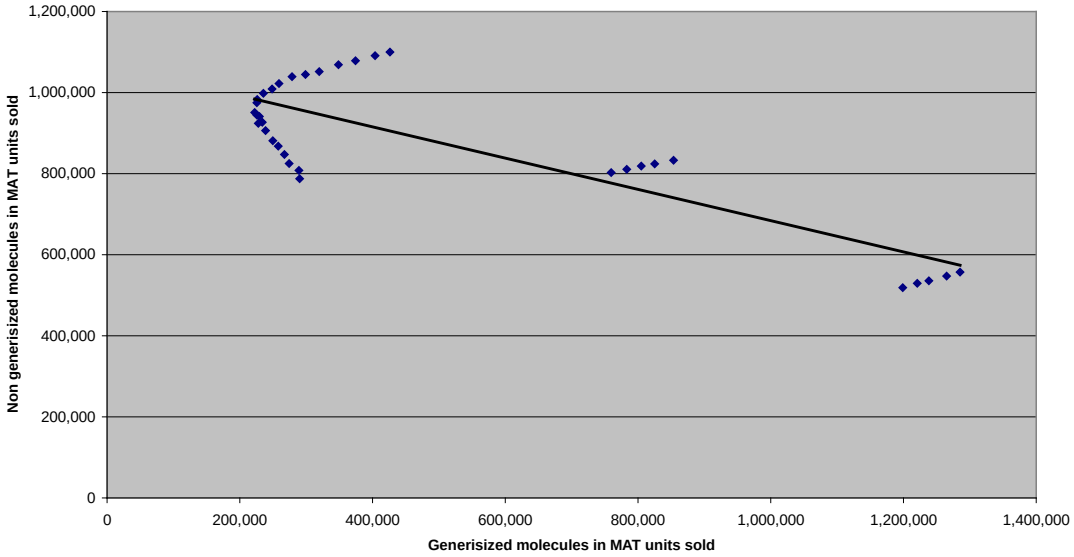
5.1 Results of descriptive analysis and measuring association

In order to determine association between generisized and non generisized molecules, moving annual totals (MAT) unit sales of the molecules were plotted on a scatter graph. This was done for each grouping, aggregate data (Figures 5, 6 and 7) and then at the molecule specific level (Figures 8, 9 and 10).

5.1.1 Aggregate data

Each point in Figure 2 is the sum of the MAT for a month of generisized molecules (x-axis) and the corresponding MAT of the non generisized molecules (y-axis). This is done so as to determine the relationship between the two MAT over the study period. The points are not in any date order as it is the trend of the sum of the two MAT over the study period which is being analyzed.

Figure 2 Linear trend between MAT of generisized PPI sold and non generisized PPI sold from August 2003 to May 2006

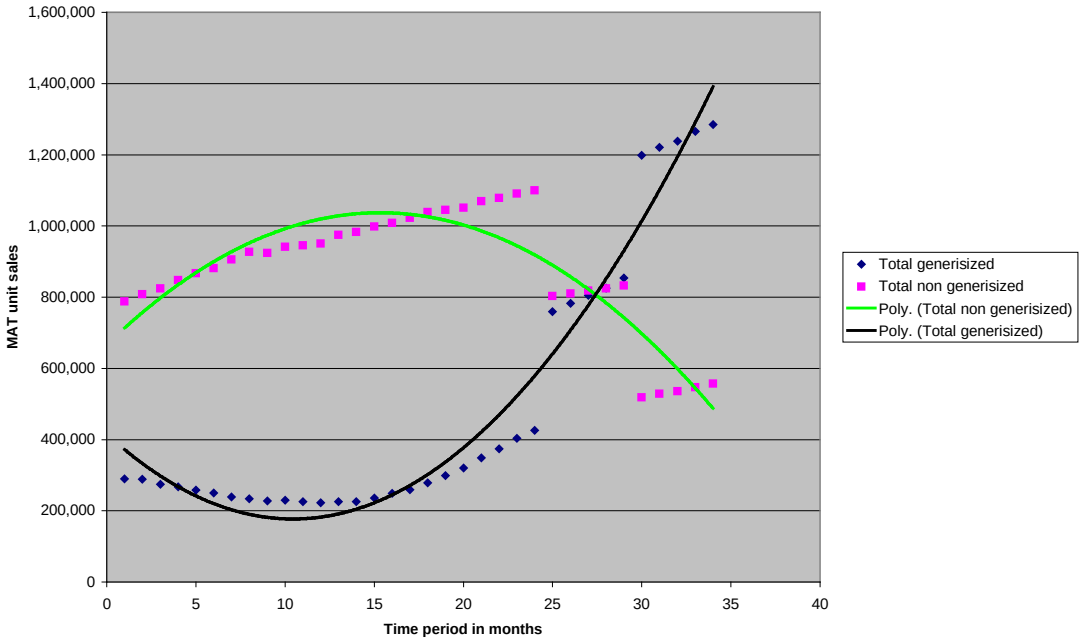


The slope of the linear trend line in Figure 2 shows that there may be some association between the two groupings although a one to one relationship between non generisized molecules and generisized molecules can be ruled out.

A one to one relationship would have meant for every non generisized molecule not sold a generisized molecule would take its place and vice a versa. If there was a one to one relationship the slope of the line would have been at 45 degrees.

Pearson's correlation coefficient for Figure 2 is -0.83 and the goodness of fit or coefficient of determination is 0.69 (Annexure 6). A correlation of 1 would imply there is a direct one to one relation between the two groups. A negative correlation implies that if one group increases the other group decreases. A goodness of fit close to or equal to 1 would have meant that points that make up the graph are in close proximity to the trend line which is not the case here. Therefore, is it hard to conclude definitively that there is a direct association between the two groups.

Figure 3 **Simultaneous polynomial MAT sales trends of generic and non generic molecules from August 2003 to May 2006**



On plotting the generisized and non generisized data as a stacked graph Figure 3 and then applying a polynomial trend line it is much easier to pick up visually, the inverse symmetry between the generisized molecules and the non generisized molecules.

Figure 4 MAT unit sales per molecule over thirty four months

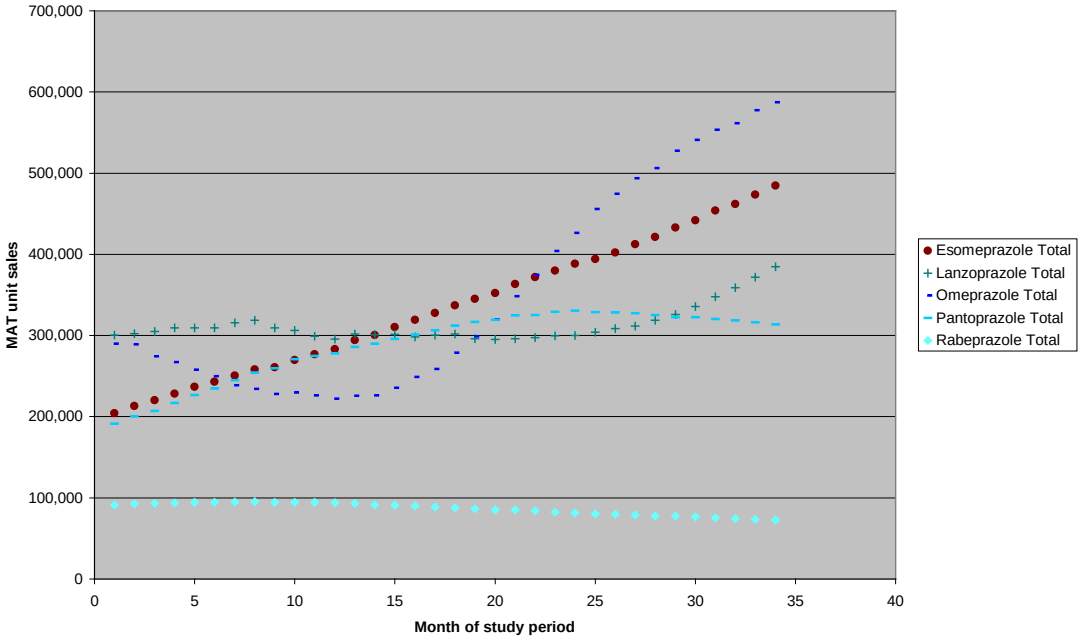


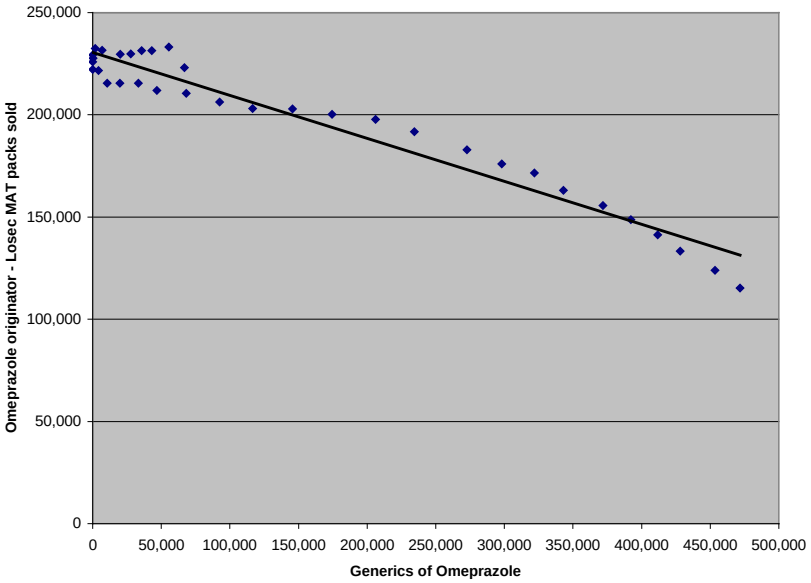
Figure 4 plots the MAT of the various molecules simultaneously over the study period. This is done to check for correlation between the molecules. There appears to be no clear correlation between molecules which implies limited therapeutic switching between any two molecules.

Esomeprazole, Omeprazole and Lanzoprazole are growing in MAT unit sales whilst Pantaprazole and Rabeprazole appear to be declining slightly.

5.1.2 Molecule specific data

Figures 5, 6 and 7 are based on the same principals as Figure 2, however, the data is summarised at the molecule level and not the aggregate level MAT.

Figure 5 Linear trend between MAT of the Omeprazole originator - Losec and generics of Omeprazole



The grouped points on the left in Figure 6 are because Lanzoprazole did not have a generic at the beginning of the study period. A generic of Lanzoprazole was launched in August 2005.

Figure 6 Linear trend between MAT of the Lanzoprazole originator - Lanzor and generic Lanzoprazole sold from August 2003 to May 2006

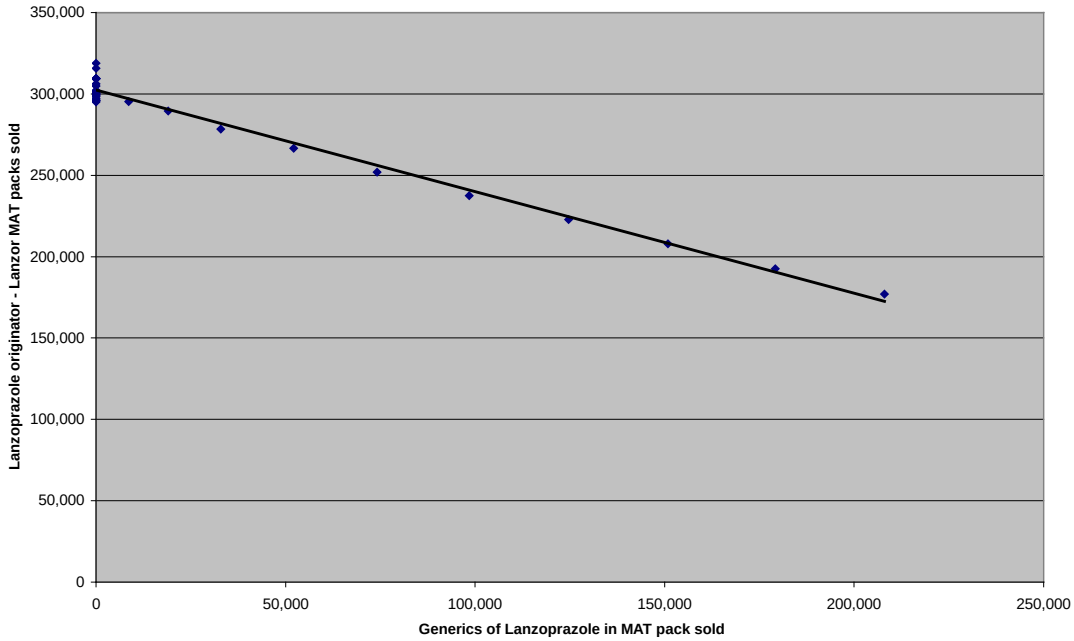
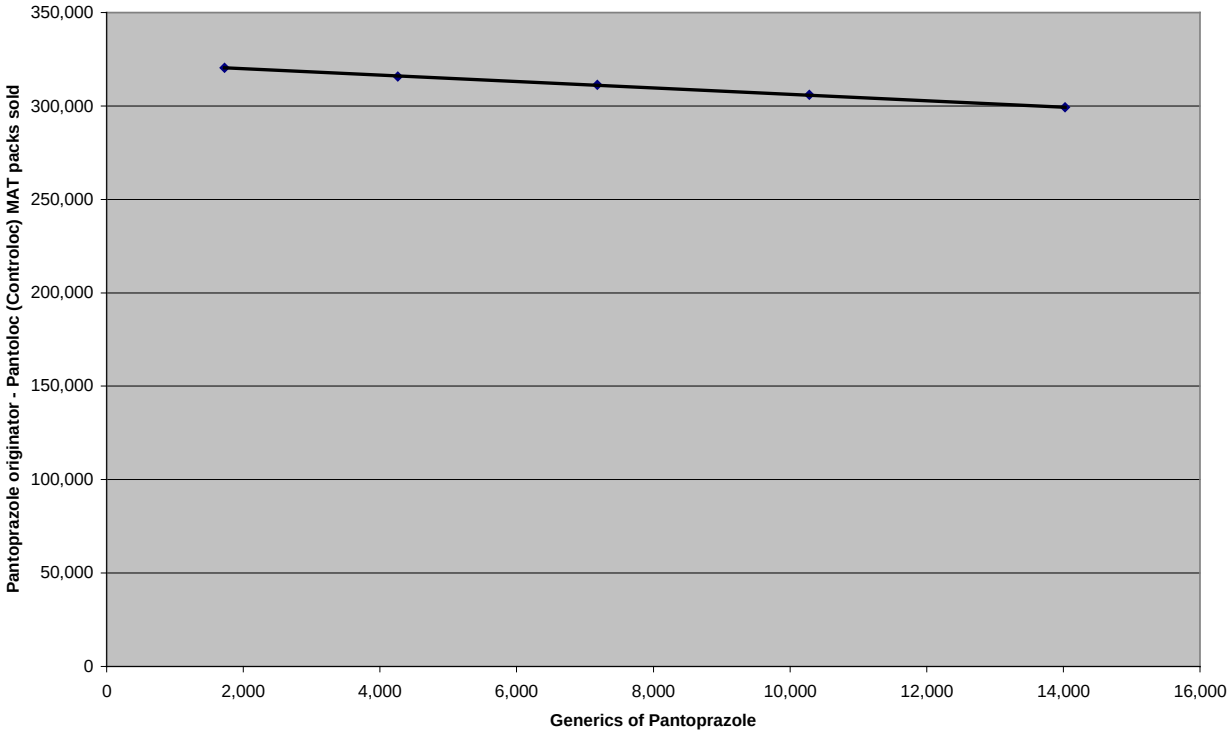


Figure 7 **Linear trend between MAT of the Pantoprazole originator - Pantoloc (Controloc) and generics of Pantoprazole sold from August 2003 to May 2006**



The above Linear trend lines, see Figures 5, 6 and 7, show that there is a degree of correlation between the generic and the non generics of the molecule as one would expect.

However, of the linear trend lines drawn in Figures 5, 6 and 7 between the originator and its generics, Omeprazole shows the closest one to one association. Therefore it appears from Figure 5 that for Omeprazole, the originator was substituted more often by its generic.

Figures 8, 9 and 10 are based on the same principals as Figure 3, however, the data is summarised at the molecule level and not the aggregate level MAT

Figure 8 **Simultaneous polynomial MAT sales trends of the Omeprazole originator - Losec and generics of Omeprazole from August 2003 to May 2006**

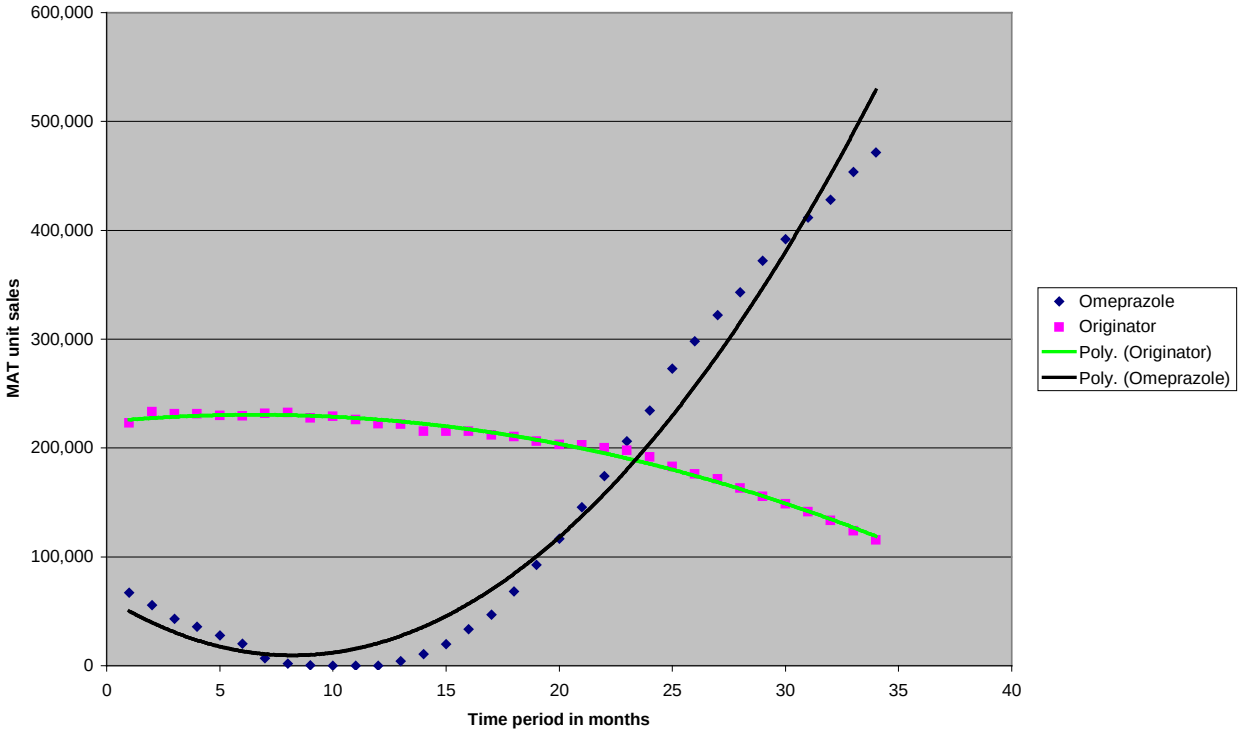


Figure 9 **Simultaneous polynomial MAT sales trends of the Lanzoprazole originator - Lanzor and generics of Lanzoprazole from August 2003 to May 2006**

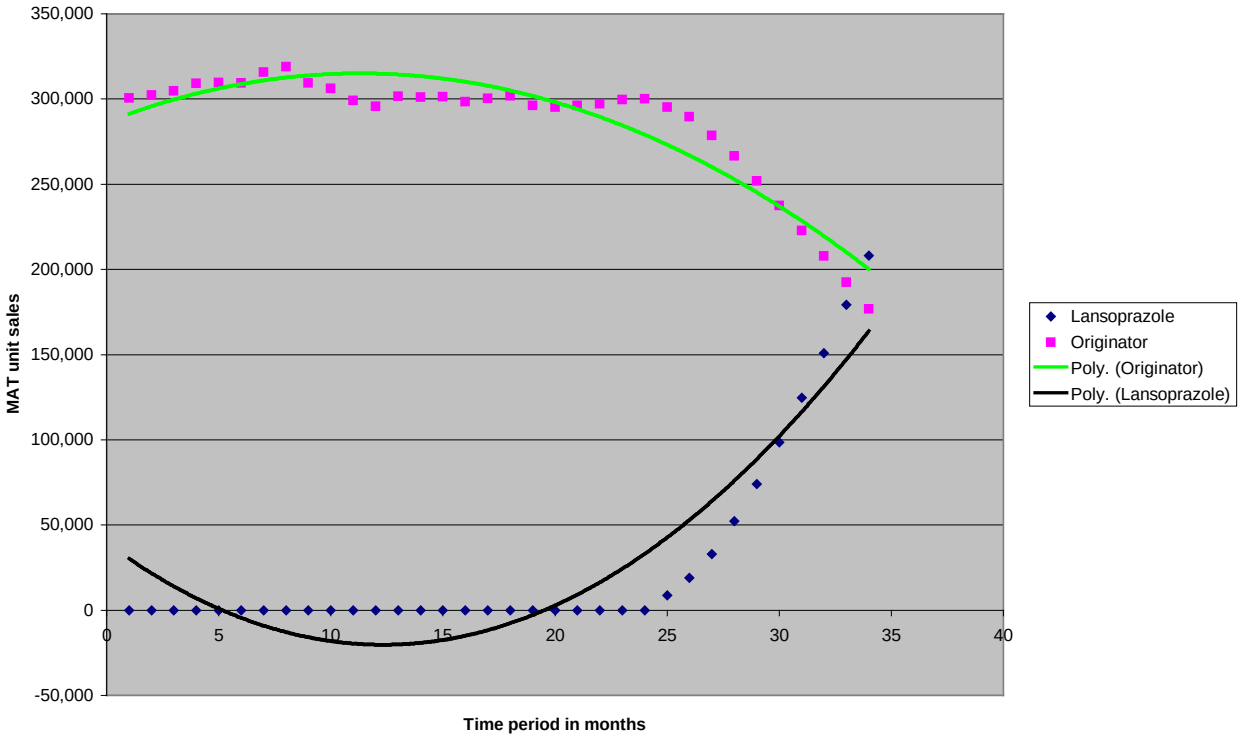
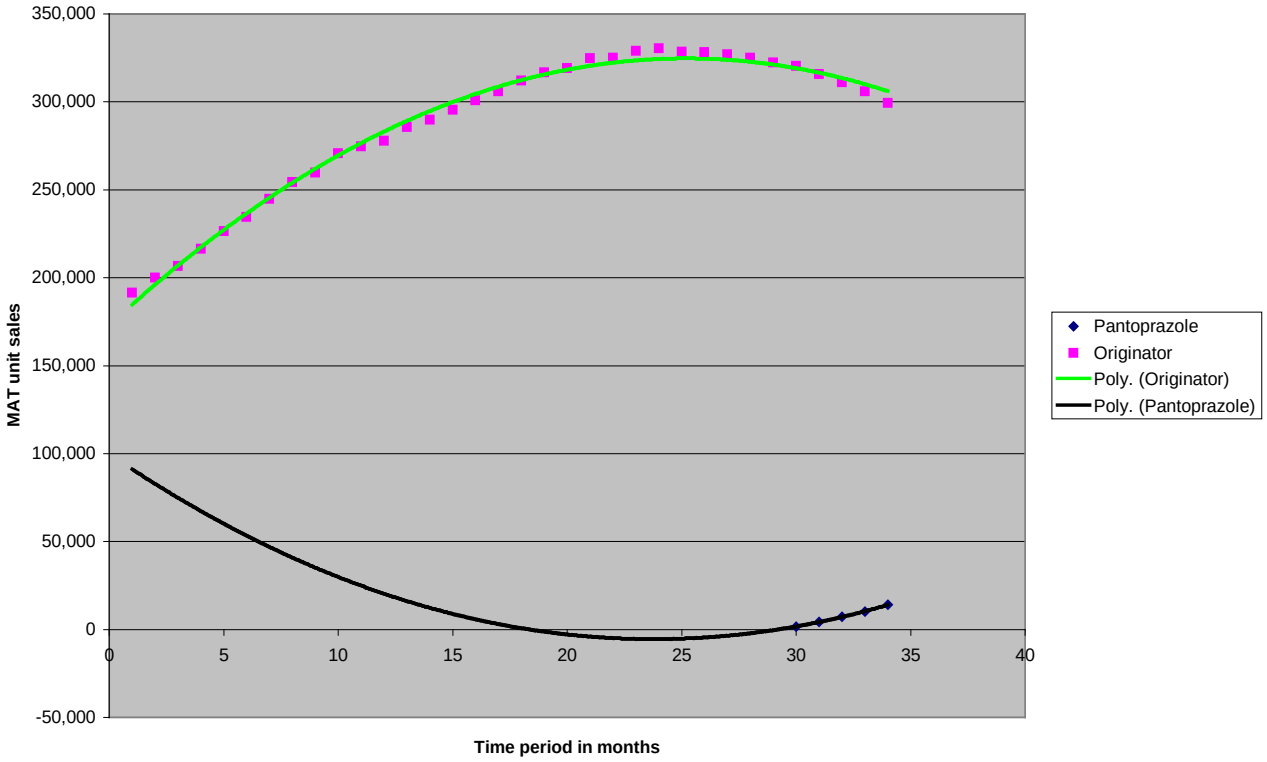


Figure 10 **Simultaneous polynomial MAT sales trends of the Pantoprazole originator and generics of Pantoprazole from August 2003 to May 2006**



When stacking the moving annual totals at the molecule level Figures 8, 9 and 10 over 34 months the symmetry observed at the aggregate level becomes more apparent indicating a potential direct correlation.

However, the trend lines in the stacked graph for the generic Omeprazole molecules (Figure 8) show that the rate of growth in sales of generics of Omeprazole is greater than the rate of loss of sales of the originator.

5.2 Results of descriptive analysis based on evolution indices

In order to determine the growth of the generic molecules, the evolution indices (EI) of the molecules were plotted on a scatter graph. This was done at the

aggregate or group level.

Each point in Figure 11 is the sum of the EI for a month of generisized molecules (x-axis) and the corresponding EI of the non generisized molecules (y-axis). This is done so as to determine the relationship between the two EIs over the study period. The points are not in any date order as it is the trend of the sum of the two EIs over the study period which is being analyzed.

A graph of the average evolution indices of the generisized molecule versus non generisized molecules to show correlation was constructed.

Figure 11 Evolution indices of market growth of generisized molecules and non generisized molecules plotted to determine correlation for the period August 2003 to May 2006

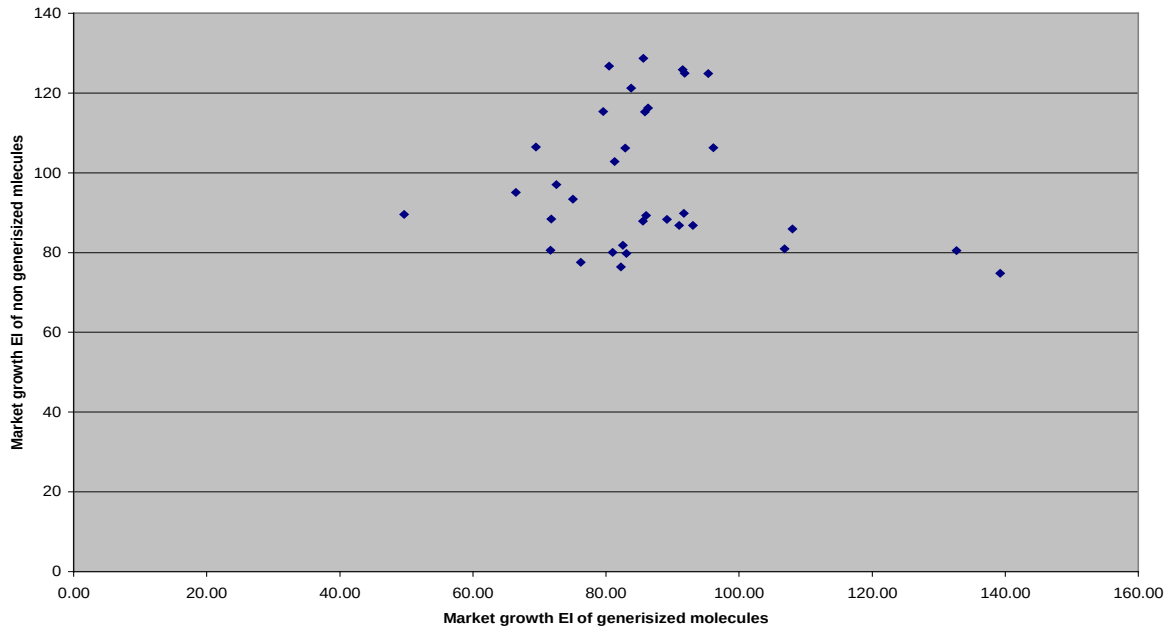
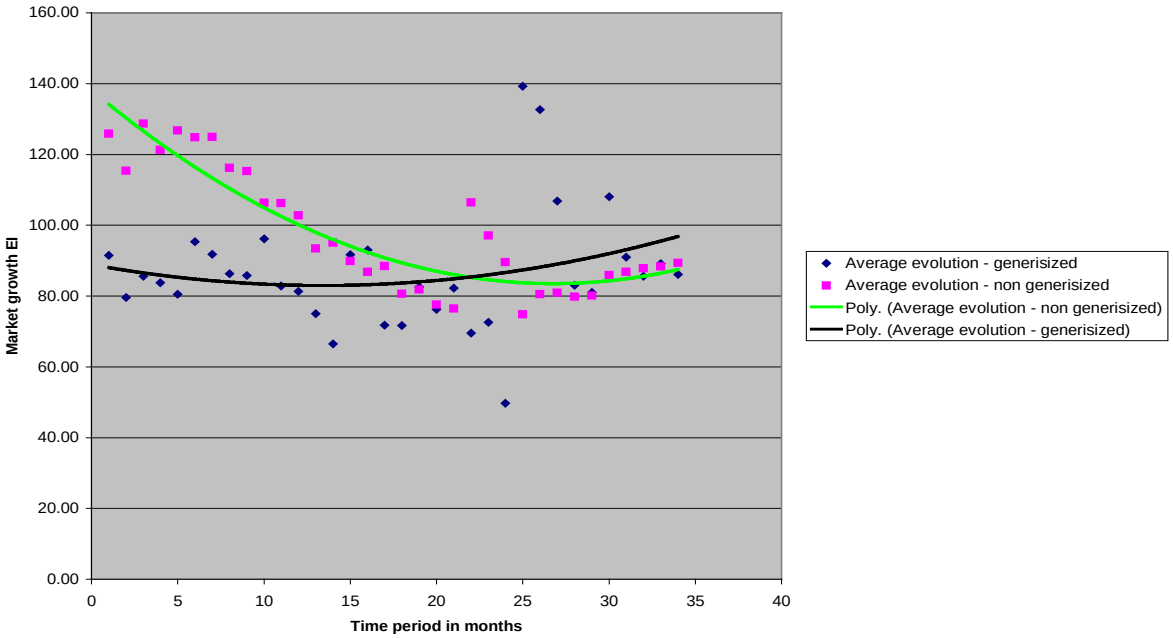


Figure 11 shows that one cannot draw a trend line as the points are not grouped but scattered.

Figure 12 **Simultaneous polynomial market growth EI trend lines of generisized and non generisized molecules between August 2003 and May 2006**



A polynomial trend line on the stacked data of average evolution indices of generic versus non generisized molecules Figure 12 however shows a decrease in the average evolution of both the generisized and non generisized molecules followed by a growth in their average evolution.

Growth of non-generisized molecules in the first 12 months remains at an average EI above 100 and then dips just below 100 as the average EI of generisized molecules starts to increase. Around month 22 of the study period the average EI of non generisized molecules dips below that of the generisized molecules, which coincides with the time when there is a strong growth of Omeprazole generics from generic manufacturers Sandoz, Adcock amd Dr. Reddy's Labs. Also at this time Lanzor is generisized taking its considerable volume although low EI into the generisized group. These two events bring the average EI's of the two groups closer together and with both EI's being below 100. However, this is misleading as the relationship of the EI between the two groups i.e. the generised and non generisized group is important and not the EI itself of a group as this is only an average in the group.

5.3 Hypothesis testing

Calculations: Refer to Annexure 7 page 4.

$$\text{Test statistic: } T = \frac{86.64-97.40-0}{\frac{\sqrt{(33x(16.76)^2 + 33x(17.28)^2)}}{\sqrt{66}}}$$

$$= -2.61$$

6 Discussion

6.1 Discussion on descriptive analysis and measuring association

At the aggregate level, there is a possibility of a switch happening from the originator molecule to the generisized molecule as the lines mirror each other which is what one would have expected see Figure 3. Mandatory substitution and the influence of medical schemes may account for this switch as discussed earlier in section 1.4.

Omeprazole in Figure 4 and Figure 8 is particularly interesting as it declines on the introduction of generics but has a subsequent sustained increase in growth with the highest share in respect of unit sales. This could be as a result of being the first molecule to be generisized in the class as well as having the highest number of me-too generics in the class.

It appears from Figure 4 that Lanzor is a strong brand despite the introduction of generics and shows growth in average EI in the last ten months of the study period. Interestingly, during this period Lanzor HB a non prescription over the counter version of Lanzor was launched. This appears to be a good marketing tactic to sustain growth when the class is being generisized. Marketing practices such the launch of a non prescription version of a non generised molecule could result in an increase in the utilization of the molecule as the patient would no longer need to visit a doctor if not on a medical scheme to obtain a PPI. This could result in a net saving to a non medical scheme member. Although in this particular study period there appears to be a switch between the Lanzor and Lanzor HB as the combined MAT remains more or less the same.

At the molecule level for Lanzoprazole and Pantarazole, i.e Figures 6 and 7 it appears that there is less correlation between the originator and its generics. However the slopes of the linear trend lines in Figure 6 and 7 are less than 45° which could imply that either both molecules are losing market share or their generics are not being accepted as equivalents.

Furthermore, the possibility of Lanzoprazole and Pantaprozole losing market share can be reinforced by:

- The polynomial trend line of the generics of Omeprazole, see Figure 8, where the generics appear to be gaining market share.
- Figure 12 where non generisized molecules appear to have an average EI greater than that of generisized molecules.

6.2 Discussion on descriptive analysis based on evolution indices

One would have expected that the generisized molecules would show a consistent upward trend in average evolution and the non generisized molecules a consistent downward trend. This expectation is true for the generisized molecules however the non generisized molecules also show an upward trend during the latter part of the study period (Figure 12). The significance of this is further tested by way of the hypothesis.

Since -2.61<-2.145, Ho is rejected and H_1 is accepted i.e. the two sample means differ significantly, $p<0.05$. The mean evolution index is less in generisized molecules than with non generisized molecules.

The results of the t-test suggest that even though the volumes of non generisized molecules prescribed reduce, the mean growth of the evolution index of these molecules is still greater then that of the generisized molecules.

This is a significant result as it has ramifications on the pharmaceutical industry and on medical schemes. For example, in the pharmaceutical industry, manufacturers of original drugs can justify marketing spend in a class that is being generisized as long as their particular molecule is patent protected to grow market share. They need not abandon their molecule. Whilst manufacturers of generic drugs need to promote therapeutic switching in addition to generic substitution to ensure that market share lost by the originator is not captured by non generisized molecules alone.

As for medical schemes, they would need to manage their risk by taking into account that their spend on non generisized molecules may increase and offset their projected savings from lower priced generics.

6.3 Reasons for difference in data and shortcomings

- During the time period from which data has been drawn for this study there was a significant change in legislation whereby the price of a medicine was fixed in the market making bonusing and discounting illegal and at the same time introducing mandatory substitution of generic medicines for non generic medicines. This would explain the poor coefficient of determination at the aggregate level on the moving annual total graphs Figure 2.
- IMS data does not take into account what the product is being used for nor does it reveal discounting practices or what the cost is to the medical aid

or patient. Therefore, there may be other factors determining the growth of non generisized molecules as well.

6.4 Explanations for the growth of non generisized molecules

Some explanations for growth of non generisized molecules might include:

- Doctors become less likely to prescribe a generisized molecule as they are no longer in control of the final brand of generic the patient is dispensed. With mandatory substitution the pharmacist is allowed to dispense any brand of medicine as long as it is a generic of the same molecule that was prescribed by the doctor. Therefore, a doctor may be more likely to prescribe a non generisized molecule to ensure that the patient is dispensed the brand the doctor wants.

- Therapeutic switching is more difficult to apply than mandatory substitution. Therapeutic switching occurs when one molecule is substituted by another molecule in the same therapeutic class. Again, a doctor in this case would prescribe a non generisized molecule so that his script is not changed by either the scheme or the pharmacist unless of course it was a 'breakthrough drug' which is not the case here.

- Doctors are not convinced of the efficacy and safety of a generic and hence will prescribe the originator or non generisized molecule. A generic of a medicine is often perceived as not being as efficacious as the originator. This may be so as doctors, pharmacists and patients do not necessarily understand the science behind the development and manufacture of a generic. Another simpler reason why a generic is considered inferior could be the perception that a more expensive product is better.

- Doctors are not sure if the generic product has been manufactured under strict manufacturing controls.

- Pharmaceutical companies look at the generisization of a molecule in a class as an opportunity to promote their non generisized molecule by marketing the integrity of their product.

- Generics are not priced much lower than the originator. Generics in South Africa are generally priced at a discount of between 20% to 30% lower than the price of the originator. Often this price differential is met by an out of pocket expense of the patient. It could also be that there is a resentment that generics are not priced at a much lower cost and therefore mandatory substitution is not enforced.

- Generics are costly. The Canadian experience [10] suggested that me-too generics increased the price of a generisized molecule. This phenomenon may be due to that after the launch of multiple generics over a period of time one may forget the originator and its price. Once this happens the individual is more likely to accept a price that increases regularly with inflation regardless of the fact that the API may have become cheaper and the manufacturing efficiency gains could be greater then inflation. Additionally, in South Africa as more me-too generics are launched manufacturers of generic medicines have adopted a strategy to brand their generics. Branded generics require promotional spend which in turns contributes to the maintenance of higher prices.

- There is a perception that a generisized drug is old technology regardless of when the patent was actually filed of the originator molecule. A newer molecule could have been bought into South Africa and started its period of exclusivity whilst an older molecule could have been brought later into South Africa and would enjoy exclusivity beyond the patent expiry of the newer molecule.

6.5 Further studies

To complement and develop this study, further work to understand growth the in non generisized molecules may include:

- What happens to the price of the originator once a generic of itself has been launched?
- At what price is a generic launched?
- What would be the conclusion if this methodology was applied across all therapeutic classes in one study
- What would be the conclusion if the study was repeated with medical schemes claims data.

7 Conclusion

The results of this research topic highlight that non generisized molecules in a therapeutic class do not necessarily stop being prescribed. Data in Annexure 7 and the pursuant testing of the hypothesis suggests that their use increases at a faster pace that the generisized molecules.

This research disproves the hypothesis that mean growth in generic molecules is equal to non generisized molecules and proves that the mean evolution index is less in generisized molecules than in non generisized molecules.

This finding is unexpected. One would have assumed that with therapeutic substitution, formularies and co-payments the growth of the non generisized molecules would have been reduced.

To apply the findings of this research generally would be premature as each therapeutic class would have its own characteristics.

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Annexures

Annexure 1

IMS data sample sheet

NEW PRODUCTS–LEADING PRODUCTS BY VALUE

RANKINGS M.0-24. MAT	RANKINGS M.0-24. MON	RANKINGS M.0-12. MAT	RANKINGS M.0-12. MON	PRODUCTS	T.C.	NO MON	NO PAC	PRODUCTS 0-12 MONTHS OLD MONTH VALUES + 000	MONTH % MAN.	MONTH % N.P.	M.A.T. VALUES + 000	M.A.T. % MAN.	M.A.T. % N.P.	PRODUCTS 0-24 MONTHS OLD MONTH VALUES + 000	MONTH % MAN.	MONTH % N.P.	M.A.T. VALUES + 000	M.A.T. % MAN.	M.A.T. % N.P.	N.P. AVER. PRICE	T.C. AVER. PRICE
160				MUCOSPECT	AOT R05C	14	4										288	0.1	0.0	24.58	21.58
161	191			CO-CODAMOL	CD8 N02B	23	2							7	0.0	0.0	287	0.1	0.0	16.15	47.99
162	81	72	38	DUOVIR	CD8 J05C	3	1	153	0.9	0.4	283	0.1	0.1	153	0.9	0.2	283	0.1	0.0	275.00	305.93
163	140	73	70	DE WITTS K & B	GU/ G04B	12	3	37	3.1	0.1	270	2.1	0.1	37	3.1	0.1	270	2.1	0.0	9.79	48.34
164	146	74	72	SENSIGEL	HEX A01A	11	1	32	0.2	0.1	269	0.1	0.1	32	0.2	0.0	269	0.1	0.0	26.67	19.25
165				SYNERCID	AVS J01F	22	1										268	0.0	0.0	476.51	103.35
166	117	75	55	ROXIFEN	GU/ M01A	7	1	68	5.8	0.2	266	2.1	0.1	68	5.8	0.1	266	2.1	0.0	94.00	94.91
167	77	76	35	ELIDEL	NVR D11A	3	3	156	0.5	0.5	263	0.1	0.1	156	0.5	0.2	263	0.1	0.0	208.79	34.30
168	168			ENSURE PLUS	ABT V06D	15	4							19	0.2	0.0	254	0.1	0.0	14.14	24.19
169	183	77	94	RIOWORM	PPN P01B	12	2	10	0.0	0.0	231	0.1	0.1	10	0.0	0.0	231	0.1	0.0	21.33	15.96
170	171			STOP-ALLERG	GNO S01G	24	1							16	3.1	0.0	230	4.6	0.0	26.85	26.07
171	162			MEPYRADERM	BE- D04A	16	1							22	0.2	0.0	229	0.1	0.0	47.22	16.67
172	163	78	82	PHOSOFORTE	PD7 A05B	6	2	22	0.7	0.1	227	0.7	0.1	22	0.7	0.0	227	0.7	0.0	19.44	56.54
173	153	79	77	ELGYFLOUR	HEX A01A	11	1	28	0.2	0.1	221	0.1	0.1	28	0.2	0.0	221	0.1	0.0	25.19	19.28
174				SINU-MED	AOT R01B	14	2										213	0.1	0.0	17.28	29.12
175	181			M-RELIEF	AOT M02A	14	1							11	0.1	0.0	212	0.1	0.0	25.80	27.82
176	207			UFT	BSE L01B	23	1							2	0.0	0.0	212	0.1	0.0	3317.16	83.10
177	130	80	65	MERCK-DOXAZOSIN	M/G C02A	5	2	52	0.8	0.2	202	0.2	0.1	52	0.8	0.1	202	0.2	0.0	82.57	160.65
178	141	81	71	PRIORIX	GSK J07B	7	1	36	0.1	0.1	196	0.0	0.1	36	0.1	0.1	196	0.0	0.0	110.62	112.19
179	158			BETANOID N	A&G D07B	22	2							26	0.0	0.0	195	0.0	0.0	18.20	102.69
180	177			PROSTCARE	AOT G04C	14	2							14	0.1	0.0	194	0.1	0.0	83.01	212.14
181				CELANCE	LLY N04A	20	2										191	0.1	0.0	361.13	303.07
182	172	82	88	FRAXONE	M/G J01D	5	2	15	0.2	0.0	189	0.2	0.1	15	0.2	0.0	189	0.2	0.0	75.40	158.71
183	196			MIDACUM	HEX N01A	14	2							6	0.0	0.0	179	0.1	0.0	96.09	217.48
184	120	83	58	ADCO-DOXAZOSIN	AOJ C02A	4	3	64	0.2	0.2	176	0.1	0.1	64	0.2	0.1	176	0.1	0.0	76.98	160.65
185	182			EMZACLEAR	SDZ D11A	13	1							10	0.1	0.0	173	0.1	0.0	41.37	34.73
186	180			OXYSPAS	CD8 G04B	20	1							11	0.1	0.0	173	0.1	0.0	252.66	47.94
187	164	84	83	ELUGEL	HEX A01A	11	1	21	0.1	0.1	167	0.1	0.1	21	0.1	0.0	167	0.1	0.0	22.43	19.31
188				DILUCORT	AOT D07A	14	2										165	0.0	0.0	18.64	40.92
189	151	85	75	KEFOTAX	SDZ J01D	7	4	29	0.2	0.1	148	0.1	0.1	29	0.2	0.0	148	0.1	0.0	275.40	158.61
190	165	86	84	MERCK-MEBEVERINE	M/G A03A	12	3	21	0.3	0.1	146	0.1	0.1	21	0.3	0.0	146	0.1	0.0	115.08	50.11
191	152	87	76	MERCK-OXYBUTYNIN	M/G G04B	12	3	29	0.4	0.1	142	0.1	0.1	29	0.4	0.0	142	0.1	0.0	241.14	47.95
192	173	88	89	DOXY CO	GU/ N02B	12	3	15	1.3	0.0	140	1.1	0.1	15	1.3	0.0	140	1.1	0.0	91.13	47.95
193				CALMOLIN ADD	AOT A11A	14	2										136	0.0	0.0	75.31	46.87
194	135	89	68	SINOPREN	RBY C09A	5	3	49	0.7	0.1	130	0.1	0.1	49	0.7	0.1	130	0.1	0.0	45.56	99.61
195	179	90	93	DYNAFLOC	PD7 J01G	7	4	11	0.4	0.0	127	0.4	0.1	11	0.4	0.0	127	0.4	0.0	88.44	124.89
196	187			WARTNER	PMP D11A	13	1							9	0.5	0.0	125	1.9	0.0	65.00	34.66
197	192			PRIMEVE PLUS NAT	GEO G02X	18	3							6	0.5	0.0	124	0.9	0.0	56.06	104.31
198	190			INFLACOR	SDZ R03D	13	3							7	0.1	0.0	122	0.1	0.0	75.49	155.57
199	188			RHINOFREE	ALC R01A	20	1							8	0.3	0.0	116	0.3	0.0	57.41	56.86
200	175	91	90	CILEST	JAN G03A	11	1	14	0.1	0.0	112	0.0	0.0	14	0.1	0.0	112	0.0	0.0	48.46	56.93
201	121	92	59	CIPLA-LAMIVUDINE	CD8 J05C	3	1	64	0.4	0.2	100	0.0	0.0	64	0.4	0.1	100	0.0	0.0	115.12	306.12
202	195			GULF ASPIRIN	GU/ N02B	18	1							6	0.5	0.0	100	0.8	0.0	99.00	47.95
203				FEMOLIN PMS	AOT A11A	14	2										97	0.0	0.0	84.93	46.88
204				TRIOPLEX EXPECTAVI	AOT A11A	14	2										97	0.0	0.0	60.29	46.89
205				TRIOMIN	A&G J01A	14	1										89	0.0	0.0	174.46	256.81
206	155	93	78	POLLENTYME	PD7 R06A	5	2	27	0.9	0.1	83	0.2	0.0	27	0.9	0.0	83	0.2	0.0	43.49	69.19
207				TRIOPLEX MULTIVIT	AOT A11A	14	1										80	0.0	0.0	49.80	46.90
208	197			BAYER ASPIRIN PL C	BAY N02B	21	2							5	0.0	0.0	79	0.0	0.0	20.35	47.96
209	184	94	95	CROMABAK	GNO S01G	7	1	10	1.9	0.0	78	1.6	0.0	10	1.9	0.0	78	1.6	0.0	52.88	26.05
210	170	95	87	INFANRIX DTPAHB	GSK J07B	7	1	17	0.0	0.0	72	0.0	0.0	17	0.0	0.0	72	0.0	0.0	200.00	111.94
211	211	96	105	RIMSTAR	SDZ J04A	3	3	2	0.0	0.0	72	0.0	0.0	2	0.0	0.0	72	0.0	0.0	68.62	46.77
212	166	97	85	STAVIR	CD8 J05C	6	2	21	0.1	0.1	71	0.0	0.0	21	0.1	0.0	71	0.0	0.0	27.04	306.91
213	204			BLEPHADOSIS	GNO S01X	21	1							3	0.6	0.0	64	1.3	0.0	47.25	601.15
214	199			NAN 3	NES V06C	13	1							4	0.3	0.0	61	0.3	0.0	31.79	42.28
215	216	98	107	H/TONES COLD&FLU	AOT R05A	11	1	1	0.0	0.0	60	0.0	0.0	1	0.0	0.0	60	0.0	0.0	37.00	35.46
216	218	99	109	H/TONES IMMUNE BOO	AOT A13A	11	1	0	0.0	0.0	56	0.0	0.0	0	0.0	0.0	56	0.0	0.0	37.00	46.47
217	202			SYMADIN	CX- J05B	20	1							3	100	0.0	51	99.8	0.0	79.38	234.69
218	215			CIPOFIX	CD8 J01D	21	2							1	0.0	0.0	49	0.0	0.0	136.30	158.63
219	201	100	101	DENTO-PLAQUE	HEX A01A	11	1	3	0.0	0.0	44	0.0	0.0	3	0.0	0.0	44	0.0	0.0	25.46	19.33
220				TRIOPLEX KIDDIVIT	AOT A11A	14	1										38	0.0	0.0	25.60	46.92
221	213			MODULEN	NES A03G	24	1							1	0.1	0.0	34	0.2	0.0	1320.00	415.00
222	203			PREGNE CREME	GEO D11A	22	1							3	0.3	0.0	34	0.3	0.0	98.00	34.75
223				TOPSITON	AOT A13A	14	1										32	0.0	0.0	27.06	46.48
224				SINUGESIC	AOT R05A	14	1										30	0.0	0.0	20.99	35.46
225	226			MATERNA	WSA A11A	22	1							0	0.0	0.0	28	0.0	0.0	49.75	46.90
226				TRITAR	AOT D05A	14	1										27	0.0	0.0	34.29	55.11
227	205			CYCLOSON CYCLOCAPS	SDZ R03D	23	3							3	0.0	0.0	25	0.0	0.0	103.64	155.32
228	219			CYBUTOL CYCLOCAPS	SDZ R03A	23	2							0	0.0	0.0	25	0.0	0.0	56.19	36.52
229	189	101	97	AZOPTIC	ALC S01E	4	1	8	0.2	0.0	24	0.1	0.0	8	0.2	0.0	24	0.1	0.0	103.03	124.07
230	200	102	100	OTRISALINE	NV- R01A	5	1	4	0.1	0.0	22	0.0	0.0	4	0.1	0.0	22	0.0	0.0	20.30	56.88
231				OROSEPT	AOT R02A	14	1										22	0.0	0.0	23.10	27.45
232	209			CLENIL	SDZ R01A	21	2							2	0.0	0.0	19	0.0	0.0	201.01	56.86
233	222			CYCLOHALER	SDZ R03I	23	1							0	0.0	0.0	17	0.0	0.0	41.53	66.40
234	194			CATEXAN	BG. C03A	18	1							6	0.6	0.0	17	0.5	0.0	46.49	128.23
235	208	103	102	MERCK-METOCLOPRAM	M/G A03F	5	1	3	0.0	0.0	16	0.0	0.0	3	0.0	0.0	16	0.0	0.0	194.76	62.23
236				SEPTISOOTH	AOT D08A	14	1										14	0.0	0.0	15.59	13.68
237	178	104	91	HARMONET	WSA G03A	1	1	14	0.1	0.0	14	0.0	0.0	14	0.1	0.0	14	0.0	0.0	59.50	56.92
238	218	105	106	DR MOM HERB COUGH	BTH R05F	11	3	2	0.2	0.0	13	0.1	0.0	2	0.2	0.0	13	0.1	0.0	19.68	20.40
239				ULCAID	AOT A02B	14	2										13	0.0	0.0	19.03	182.09

Annexure 2

Basic Pharmaceutical Patents in South Africa which expire in 2000 onwards. Specifically, Proton Pump Inhibitors.

Pharmaceutical Patent	**Patent number**	**Date of expiry**
Omeprazole process	83/5143	14.07.2003
Omeprazole salts	84/1202	17.02.2004
Omeprazole composition	87/2378	01.04.2007
Omeprazole composition with antibiotic	93/2364	01.04.2013
Omeprazole crystalline form	98/11174	07.12.2018
Pantoprazole	85/4287	06.06.2005

Annexure 3

New Proton Pump Inhibitors launched between October 2003 and September 2005

Product	Date Launched
ADCO-OMEPRAZOLE	September-04
SANDOZ OMEPRAZOLE	August-04
ALTOSEC	January-05
OMEZ	July-04
LANZOR HB	April-04
OMILOC	January-05
LANSOLOC	August-05
ADCO-ROZNAL	August-05
NOZER	October-06
ASPEN-LANZOPRAZOLE	November-06
TOPOZOLE	January-06

Annexure 4

Opinion on suitability of statistical method

ClinStat CC

Reg No CK 96/35541/23

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Dear Mr Mangalmurti,

This is to confirm that I reviewed your Research Protocol entitled "A retrospective analysis of the unit growth of non-generisized proton pump inhibitors after the launch of generic molecules in the therapeutic class".

The t test that you propose is a suitable test for the comparison of two mean values from two independent samples, and would be applicable at each of the time points of your dataset. I am also investigating other possible statistical techniques for the comparison of the two groups over time, and will communicate with you later in this regard.

Yours sincerely,

Prof HS Schoeman
Biostatistician

22 February 2006

Annexure 5

Ethics approval

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)

Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

PC-J/527dsk16es

29 March 2006

TO WHOM IT MAY CONCERN:

Student: **Mr Ajit Mangalmurti**

Degree: **MSc (Med) Pharmaceutical Affairs**

Protocol: **A retrospective analysis of the growth of non generisized proton pump inhibitors after the launch of generic molecules in the therapeutic class**

This certifies that this project does not require clearance from the Human Research Ethics Committee (Medical). The study involves the analysis of public domain information and no human subjects are involved.

Yours faithfully

Professor Peter Cleaton-Jones
Chair: Human Research Ethics Committee (Medical)

copy: Anisa Keshav, Research Office, Senate House, Wits

Annexure 6 Raw data on moving annual totals and calculation of Pearsons correlation coefficient and coefficient of determination

	TC IV DESC	**MAT ~ 08/2003**	**MAT ~ 09/2003**	**MAT ~ 10/2003**	**MAT ~ 11/2003**	**MAT ~ 12/2003**	**MAT ~ 01/2004**	**MAT ~ 02/2004**	**MAT ~ 03/2004**
	Non generisized								
l	LANZOR S.A	300,606	302,207	304,852	309,257	309,621	309,438	315,733	318,932
e	NEXIAM AZN	204,101	213,232	220,101	228,107	236,641	242,824	250,577	258,323
p	PANTOLOC AMU	136,035	142,648	147,600	155,475	163,827	169,633	177,612	184,815
r	PARIET JAN	91,579	92,872	93,081	93,513	94,613	94,348	95,029	95,570
p	CONTROLOC AMU	55,441	57,363	59,116	61,033	62,718	64,819	67,077	69,501
l	LANZOR HB S.A	0	0	0	0	0	0	0	0
	Total non generisized	**787,762**	**808,322**	**824,750**	**847,385**	**867,420**	**881,062**	**906,028**	**927,141**
	Generisized								
o	ULZEC TR/	66,949	55,611	42,998	35,729	27,841	20,045	6,866	1,736
o	LOSEC AZN	66,465	76,821	75,669	75,528	73,911	74,287	73,472	73,485
o	OMEZ DRL	0	0	0	0	0	0	0	0
o	SANDOZ OMEPRAZOLE SDZ	0	0	0	0	0	0	0	0
o	ADCO-OMEPRAZOLE AOJ	0	0	0	0	0	1	1	1
o	ALTOSEC A&G	0	0	0	0	0	0	0	0
o	OMILOC HEX	0	0	0	0	0	0	0	0
l	ADCO-ROZNAL AOJ	0	0	0	0	0	0	0	0
l	LANSOLOC CD8	0	0	0	0	0	0	0	0
o	NOZER BE-	0	0	0	0	0	0	0	0
l	ASPEN-LANSOPRAZOLE A&G	0	0	0	0	0	0	0	0
p	TOPZOLE AOJ	0	0	0	0	0	0	0	0
l	LANZOR S.A								
l	LANZOR HB S.A								
p	PANTOLOC AMU								
p	CONTROLOC AMU								
o	LOSEC MUPS AZN	156,605	156,390	155,732	155,937	155,972	155,287	158,196	158,910

Annexure 6 Raw data on moving annual totals and calculation of Pearsons correlation coefficient and coefficient of determination

	TC IV DESC	**MAT ~ 04/2004**	**MAT ~ 05/2004**	**MAT ~ 06/2004**	**MAT ~ 07/2004**	**MAT ~ 08/2004**	**MAT ~ 09/2004**	**MAT ~ 10/2004**	**MAT ~ 11/2004**
	Non generisized								
l	LANZOR S.A	309,321	304,508	295,059	288,739	289,507	283,994	279,644	271,651
e	NEXIAM AZN	260,818	269,938	276,855	282,966	294,183	300,678	310,234	319,427
p	PANTOLOC AMU	189,102	198,642	202,175	205,429	212,461	216,460	221,316	226,076
r	PARIET JAN	94,584	94,656	94,354	94,032	93,136	91,261	90,834	90,129
p	CONTROLOC AMU	70,558	72,027	72,523	72,458	73,139	73,424	74,174	74,773
l	LANZOR HB S.A	0	1,627	4,004	6,910	12,151	17,140	21,793	26,760
	Total non generisized	**924,383**	**941,398**	**944,970**	**950,534**	**974,577**	**982,957**	**997,995**	**1,008,816**
	Generisized								
o	ULZEC TR/	265	119	91	78	50	42	38	20
o	LOSEC AZN	72,206	74,020	72,465	71,416	71,222	67,596	69,942	72,464
o	OMEZ DRL	0	0	0	0	1,317	2,936	5,111	7,772
o	SANDOZ OMEPRAZOLE SDZ	0	0	0	0	2,731	5,580	9,545	14,697
o	ADCO-OMEPRAZOLE AOJ	1	1	1	1	1	2,091	5,236	10,891
o	ALTOSEC A&G	0	0	0	0	0	0	0	0
o	OMILOC HEX	0	0	0	0	0	0	0	0
l	ADCO-ROZNAL AOJ	0	0	0	0	0	0	0	0
l	LANSOLOC CD8	0	0	0	0	0	0	0	0
o	NOZER BE-	0	0	0	0	0	0	0	0
l	ASPEN-LANSOPRAZOLE A&G	0	0	0	0	0	0	0	0
p	TOPZOLE AOJ	0	0	0	0	0	0	0	0
l	LANZOR S.A								
l	LANZOR HB S.A								
p	PANTOLOC AMU								
p	CONTROLOC AMU								
o	LOSEC MUPS AZN	155,442	155,260	153,395	150,743	150,474	147,861	145,470	143,061

	TC IV DESC	**MAT ~ 12/2004**	**MAT ~ 01/2005**	**MAT ~ 02/2005**	**MAT ~ 03/2005**	**MAT ~ 04/2005**	**MAT ~ 05/2005**	**MAT ~ 06/2005**	**MAT ~ 07/2005**
	Non generisized								
l	LANZOR S.A	268,336	265,806	255,743	249,204	245,022	242,083	239,438	236,919
e	NEXIAM AZN	327,763	337,081	345,120	352,273	363,176	371,911	379,967	388,490
p	PANTOLOC AMU	230,182	235,878	240,855	243,527	248,204	248,315	253,009	254,321
r	PARIET JAN	88,512	87,979	86,706	84,941	84,990	84,170	82,667	81,375
p	CONTROLOC AMU	75,903	76,210	75,888	75,710	76,485	76,682	75,982	76,092
l	LANZOR HB S.A	31,976	35,999	40,386	45,873	51,232	55,181	60,118	63,075
	Total non generisized	**1,022,672**	**1,038,953**	**1,044,698**	**1,051,528**	**1,069,109**	**1,078,342**	**1,091,181**	**1,100,272**
	Generisized								
o	ULZEC TR/	12	5	3	3	3	0	0	0
o	LOSEC AZN	72,990	74,182	76,685	78,744	82,378	83,772	86,242	84,551
o	OMEZ DRL	10,777	14,556	18,148	21,716	25,602	29,188	32,830	36,392
o	SANDOZ OMEPRAZOLE SDZ	18,690	22,260	26,578	30,917	36,898	43,083	51,610	62,514
o	ADCO-OMEPRAZOLE AOJ	17,398	28,316	38,699	48,265	59,179	70,431	80,348	84,011
o	ALTOSEC A&G	0	3,057	7,877	13,047	18,503	22,977	29,243	35,552
o	OMILOC HEX	0	0	1,143	2,682	5,320	8,687	12,199	16,022
l	ADCO-ROZNAL AOJ	0	0	0	0	0	0	0	0
l	LANSOLOC CD8	0	0	0	0	0	0	0	0
o	NOZER BE-	0	0	0	0	0	0	0	0
l	ASPEN-LANSOPRAZOLE A&G	0	0	0	0	0	0	0	0
p	TOPZOLE AOJ	0	0	0	0	0	0	0	0
l	LANZOR S.A								
l	LANZOR HB S.A								
p	PANTOLOC AMU								
p	CONTROLOC AMU								
o	LOSEC MUPS AZN	138,894	136,263	129,530	124,371	120,526	116,414	111,554	107,183

	TC IV DESC	**MAT ~ 08/2005**	**MAT ~ 09/2005**	**MAT ~ 10/2005**	**MAT ~ 11/2005**	**MAT ~ 12/2005**	**MAT ~ 01/2006**	**MAT ~ 02/2006**	**MAT ~ 03/2006**
	Non generisized								
l	LANZOR S.A								
e	NEXIAM AZN	394,356	402,122	412,558	421,376	432,830	441,879	453,781	461,705
p	PANTOLOC AMU	252,822	253,522	252,997	252,060	250,115			
r	PARIET JAN	80,347	79,919	79,069	77,646	77,710	76,740	75,316	74,299
p	CONTROLOC AMU	75,581	74,768	74,108	72,985	72,286			
l	LANZOR HB S.A								
	Total non generisized	**803,106**	**810,331**	**818,732**	**824,067**	**832,941**	**518,619**	**529,097**	**536,004**
	Generisized								
o	ULZEC TR/	0	0	0	0	0	0	0	0
o	LOSEC AZN	81,109	77,538	75,902	70,367	64,942	60,532	55,176	49,159
o	OMEZ DRL	39,076	41,018	42,608	44,212	45,652	46,251	47,026	47,372
o	SANDOZ OMEPRAZOLE SDZ	73,300	80,191	86,605	88,519	91,301	94,042	95,027	97,879
o	ADCO-OMEPRAZOLE AOJ	95,926	100,759	104,992	109,889	118,183	118,873	120,923	124,550
o	ALTOSEC A&G	43,952	51,862	60,990	72,860	88,440	103,675	118,529	127,478
o	OMILOC HEX	20,589	24,386	26,746	26,842	26,848	26,860	26,943	26,855
l	ADCO-ROZNAL AOJ	1,522	2,697	4,187	5,437	6,622	9,416	10,639	12,491
l	LANSOLOC CD8	7,126	16,315	28,768	46,024	66,033	86,117	109,171	132,511
o	NOZER BE-	5	5	5	789	1,502	2,346	3,366	3,874
l	ASPEN-LANSOPRAZOLE A&G	0	0	0	727	1,479	2,906	4,884	5,840
p	TOPZOLE AOJ	0	0	0	0	0	1,726	4,259	7,178
l	LANZOR S.A	231,564	225,314	215,266	204,393	192,191	179,798	166,879	154,735
l	LANZOR HB S.A	63,747	64,263	63,224	62,228	59,799	57,610	56,012	53,153
p	PANTOLOC AMU						249,135	245,887	243,402
p	CONTROLOC AMU						71,363	69,791	67,797
o	LOSEC MUPS AZN	101,849	98,498	95,715	92,761	90,705	88,149	86,196	84,086

	TC IV DESC	**MAT ~ 04/2006**	**MAT ~ 05/2006**
	Non generisized		
l	LANZOR S.A		
e	NEXIAM AZN	473,567	484,786
p	PANTOLOC AMU		
r	PARIET JAN	73,568	72,582
p	CONTROLOC AMU		
l	LANZOR HB S.A		
	Total non generisized	**547,135**	**557,368**
	Generisized		
o	ULZEC TR/	0	0
o	LOSEC AZN	42,258	36,128
o	OMEZ DRL	47,861	48,257
o	SANDOZ OMEPRAZOLE SDZ	99,399	100,527
o	ADCO-OMEPRAZOLE AOJ	125,689	124,910
o	ALTOSEC A&G	150,485	167,031
o	OMILOC HEX	25,689	23,863
l	ADCO-ROZNAL AOJ	13,826	15,187
l	LANSOLOC CD8	157,522	183,085
o	NOZER BE-	4,406	7,081
l	ASPEN-LANSOPRAZOLE A&G	7,805	9,742
p	TOPZOLE AOJ	10,284	14,027
l	LANZOR S.A	142,134	129,916
l	LANZOR HB S.A	50,352	46,982
p	PANTOLOC AMU	240,565	236,668
p	CONTROLOC AMU	65,305	62,576
o	LOSEC MUPS AZN	81,611	79,221

		1	2	3	4	5	6	7	8
	Total generisized	**290,019**	**288,822**	**274,399**	**267,194**	**257,724**	**249,620**	**238,535**	**234,132**
	Total non generisized	787,762	808322	824750	847385	867420	881062	906028	927141
		1,077,781	1,097,144	1,099,149	1,114,579	1,125,144	1,130,682	1,144,563	1,161,273
	Omeprazole	66,949	55,611	42,998	35,729	27,841	20,046	6,867	1,737
	Originator	223,070	233,211	231,401	231,465	229,883	229,574	231,668	232,395
	Lansoprazole	0	0	0	0	0	0	0	0
	Originator	300,606	302,207	304,852	309,257	309,621	309,438	315,733	318,932
	Pantoprazole								
	Originator	191,476	200,011	206,716	216,508	226,545	234,452	244,689	254,316

		9	10	11	12	13	14	15	16
	Total generisized	**227,914**	**229,400**	**225,952**	**222,238**	**225,795**	**226,106**	**235,342**	**248,905**
	Total non generisized	924383	941398	944970	950534	974577	982957	997995	1008816
		1,152,297	1,170,798	1,170,922	1,172,772	1,200,372	1,209,063	1,233,337	1,257,721
	Omeprazole	266	120	92	79	4,099	10,649	19,930	33,380
	Originator	227,648	229,280	225,860	222,159	221,696	215,457	215,412	215,525
	Lansoprazole	0	0	0	0	0	0	0	0
	Originator	309,321	306,135	299,063	295,649	301,658	301,134	301,437	298,411
	Pantoprazole								
	Originator	259,660	270,669	274,698	277,887	285,600	289,884	295,490	300,849

		17	18	19	20	21	22	23	24
	Total generisized	**258,761**	**278,639**	**298,663**	**319,745**	**348,409**	**374,552**	**404,026**	**426,225**
	Total non generisized	1022672	1038953	1044698	1051528	1069109	1078342	1091181	1100272
		1,281,433	1,317,592	1,343,361	1,371,273	1,417,518	1,452,894	1,495,207	1,526,497
	Omeprazole	46,877	68,194	92,448	116,630	145,505	174,366	206,230	234,491
	Originator	211,884	210,445	206,215	203,115	202,904	200,186	197,796	191,734
	Lansoprazole	0	0	0	0	0	0	0	0
	Originator	300,312	301,805	296,129	295,077	296,254	297,264	299,556	299,994
	Pantoprazole								
	Originator	306,085	312,088	316,743	319,237	324,689	324,997	328,991	330,413

Annexure 6 Raw data on moving annual totals and calculation of Pearsons correlation coefficient and coefficient of determination

		25	26	27	28	29	30	31	32
	Total generisized	**759,765**	**782,846**	**805,008**	**825,048**	**853,697**	**1,198,799**	**1,220,708**	**1,238,360**
	Total non generisized	803106	810331	818732	824067	832941	518619	529097	536004
		1,562,871	1,593,177	1,623,740	1,649,115	1,686,638	1,717,418	1,749,805	1,774,364
	Omeprazole	272,848	298,221	321,946	343,111	371,926	392,047	411,814	428,008
	Originator	182,958	176,036	171,617	163,128	155,647	148,681	141,372	133,245
	Lansoprazole	8,648	19,012	32,955	52,188	74,134	98,439	124,694	150,842
	Originator	295,311	289,577	278,490	266,621	251,990	237,408	222,891	207,888
	Pantoprazole						1,726	4,259	7,178
	Originator	328,403	328,290	327,105	325,045	322,401	320,498	315,678	311,199

		33	34
	Total generisized	**1,265,191**	**1,285,201**
	Total non generisized	547135	557368
		1,812,326	1,842,569
	Omeprazole	453,529	471,669
	Originator	123,869	115,349
	Lansoprazole	179,153	208,014
	Originator	192,486	176,898
	Pantoprazole	10,284	14,027
	Originator	305,870	299,244

					Pearson correlation coefficient	Coefficient of determination (goodness of fit)			
				Total generisized	**-0.831633**	**0.691613**			
				Omeprazole	**-0.973349**	**0.947407**			
				Lansoprazole	**-0.988142**	**0.976424**			
				Pantoprazole	**-0.999645**	**0.999291**			

Annexure 6 Raw data on moving annual totals and calculation of Pearsons correlation coefficient and coefficient of determination

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Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

	ACID PUMP INHIBITORS	Aug-03	Sep-03	Oct-03	Nov-03	Dec-03	Jan-04	Feb-04	Mar-04	Apr-04
	Non generisized									
l	LANZOR S.A	63.32	86.43	109.63	100.14	90.79	92.93	110.44	95.78	77.94
	NEXIAM AZN	155.84	135.93	147.42	130.48	141.65	134.51	126.21	122.31	122.82
p	PANTOLOC AMU	156.13	139.66	144.06	161.01	170.50	160.57	159.37	137.99	145.70
	PARIET JAN	101.71	95.24	100.72	89.21	102.67	90.25	95.06	89.76	96.44
p	CONTROLOC AMU	152.41	119.40	141.55	125.34	128.16	145.94	133.71	135.27	133.47
l	LANZOR HB S.A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Average evolution - non generisized	**125.88**	**115.33**	**128.68**	**121.24**	**126.75**	**124.84**	**124.96**	**116.22**	**115.27**
	Generisized									
o	ULZEC TR/	0.36	0.06	0.03	0.21	0.09	0.08	0.01	0.00	0.00
o	LOSEC AZN	0.00	0.00	78.25	81.84	71.25	102.31	75.19	83.97	86.36
o	OMEZ DRL	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
o	SANDOZ OMEPRAZOLE SDZ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
o	ADCO-OMEPRAZOLE AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
o	ALTOSEC A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
o	OMILOC HEX	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
l	ADCO-ROZNAL AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
l	LANSOLOC CD8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
o	NOZER BE-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
l	ASPEN-LANSOPRAZOLE A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
p	TOPZOLE AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
l	LANZOR S.A									
l	LANZOR HB S.A									
p	PANTOLOC AMU									
p	CONTROLOC AMU									
o	LOSEC MUPS AZN	91.52	79.60	92.98	85.70	89.67	88.41	108.42	88.71	85.30
	Average evolution - generisized	**91.52**	**79.6**	**85.615**	**83.77**	**80.46**	**95.36**	**91.805**	**86.34**	**85.83**

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

ACID PUMP INHIBITORS	May-04	Jun-04	Jul-04	Aug-04	Sep-04	Oct-04	Nov-04	Dec-04	Jan-05	Feb-05	Mar-05	Apr-05	May-05
Non generisized													
LANZOR S.A	67.52	69.81	74.35	79.66	72.13	65.12	57.02	69.89	62.41	53.71	58.44	55.18	64.60
NEXIAM AZN	127.10	133.13	128.47	118.44	118.74	116.07	112.71	109.91	102.52	106.57	101.37	98.28	99.80
PANTOLOC AMU	146.94	123.64	120.02	113.93	115.65	103.95	103.20	99.70	99.09	103.54	89.97	85.16	75.04
PARIET JAN	83.23	96.45	93.96	69.13	72.17	74.49	72.82	65.51	64.96	68.44	61.49	67.57	66.40
CONTROLOC AMU	106.61	108.09	97.16	85.84	96.62	89.52	88.32	97.18	74.03	76.76	76.34	75.85	76.93
LANZOR HB S.A	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	255.87
Average evolution - non generisized	**106.28**	**106.22**	**102.79**	**93.40**	**95.06**	**89.83**	**86.81**	**88.44**	**80.60**	**81.80**	**77.52**	**76.41**	**106.44**
Generisized													
ULZEC TR/	1.66	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LOSEC AZN	111.09	78.64	82.91	74.70	59.93	119.43	122.05	87.52	89.15	120.70	105.37	118.76	89.47
OMEZ DRL	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SANDOZ OMEPRAZOLE SDZ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ADCO-OMEPRAZOLE AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ALTOSEC A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
OMILOC HEX	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ADCO-ROZNAL AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LANSOLOC CD8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NOZER BE-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ASPEN-LANSOPRAZOLE A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TOPZOLE AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LANZOR S.A													
LANZOR HB S.A													
PANTOLOC AMU													
CONTROLOC AMU													
LOSEC MUPS AZN	81.21	87.10	79.68	75.31	73.00	64.02	64.04	55.99	54.22	44.35	47.07	45.77	49.49
Average evolution - generisized	**96.15**	**82.87**	**81.3**	**75.005**	**66.465**	**91.73**	**93.05**	**71.755**	**71.69**	**82.525**	**76.22**	**82.27**	**69.48**

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

ACID PUMP INHIBITORS	Jun-05	Jul-05	Aug-05	Sep-05	Oct-05	Nov-05	Dec-05	Jan-06	Feb-06	Mar-06	Apr-06	May-06	**Pearson correlation coefficient**
Non generisized													
LANZOR S.A	62.36	65.77											
NEXIAM AZN	91.49	100.17	90.58	99.31	106.49	105.70	104.49	104.13	109.33	105.08	105.90	108.78	
PANTOLOC AMU	88.94	80.96	71.26	81.15	76.95	79.10	69.75						
PARIET JAN	57.62	61.51	66.63	73.40	69.30	66.02	77.33	67.75	64.26	70.66	70.72	69.89	
CONTROLOC AMU	63.56	76.92	70.60	68.19	70.89	68.32	68.64						
LANZOR HB S.A	218.39	152.22											
Average evolution - non generisized	**97.06**	**89.59**	**74.77**	**80.51**	**80.91**	**79.79**	**80.05**	**85.94**	**86.80**	**87.87**	**88.31**	**89.34**	**-0.1521488**
Generisized													
ULZEC TR/	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
LOSEC AZN	101.74	52.90	35.80	36.79	60.39	20.34	16.03	17.54	23.49	21.49	13.70	22.37	
OMEZ DRL	0.00	0.00	232.58	172.38	136.75	132.62	113.34	92.46	97.83	92.25	88.64	91.27	
SANDOZ OMEPRAZOLE SDZ	0.00	0.00	378.92	267.94	206.79	113.48	130.01	141.09	98.83	139.36	98.74	97.18	
ADCO-OMEPRAZOLE AOJ	0.00	0.00	0.00	259.61	185.33	154.39	174.29	84.85	96.36	115.97	86.95	76.50	
ALTOSEC A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	477.55	328.46	229.65	410.73	386.16	
OMILOC HEX	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	86.31	79.28	43.93	37.62	
ADCO-ROZNAL AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
LANSOLOC CD8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
NOZER BE-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
ASPEN-LANSOPRAZOLE A&G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
TOPZOLE AOJ	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
LANZOR S.A			58.34	53.64	39.86	37.16	32.55	30.10	28.44	30.41	27.48	28.98	
LANZOR HB S.A			86.37	86.48	61.36	66.15	40.94	36.38	51.16	40.28	37.58	32.52	
PANTOLOC AMU								75.83	68.92	74.15	68.61	67.52	
CONTROLOC AMU								67.88	60.01	57.01	49.56	48.56	
LOSEC MUPS AZN	43.39	46.42	43.53	51.92	57.36	57.28	59.86	56.74	61.31	61.11	55.11	57.89	
Average evolution - generisized	**72.57**	**49.66**	**139.26**	**132.68**	**106.8**	**83.06**	**81.003**	**108**	**91.011**	**85.542**	**89.18**	**86.052**	

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

ACID PUMP INHIBITORS	**Coefficient of determination (goodness of fit)**					
Non generisized						
LANZOR S.A						
NEXIAM AZN						
PANTOLOC AMU						
PARIET JAN						
CONTROLOC AMU						
LANZOR HB S.A						
Average evolution - non generisized	**0.023149**					
Generisized						
ULZEC TR/						
LOSEC AZN						
OMEZ DRL						
SANDOZ OMEPRAZOLE SDZ						
ADCO-OMEPRAZOLE AOJ						
ALTOSEC A&G						
OMILOC HEX						
ADCO-ROZNAL AOJ						
LANSOLOC CD8						
NOZER BE-						
ASPEN-LANSOPRAZOLE A&G						
TOPZOLE AOJ						
LANZOR S.A						
LANZOR HB S.A						
PANTOLOC AMU						
CONTROLOC AMU						
LOSEC MUPS AZN						
Average evolution - generisized						

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

	Time period	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
	Average evolution - generisized	**91.52**	**79.60**	**85.62**	**83.77**	**80.46**	**95.36**	**91.81**	**86.34**	**85.83**
	Average evolution - non generisized	**125.882**	**115.332**	**128.676**	**121.236**	**126.754**	**124.84**	**124.958**	**116.222**	**115.274**
		Hypothesis testing								
		Sample size	**Sample mean**	**Sample variance**						
		34	**86.64**	**16.735516**						
		34	**97.40**	**17.277431**						
		T statistic	**4.1251992**							
			-10.77							
			-2.609797							

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

Time period	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Average evolution - generisized	**96.15**	**82.87**	**81.30**	**75.01**	**66.47**	**91.73**	**93.05**	**71.76**	**71.69**	**82.53**	**76.22**	**82.27**	**69.48**
Average evolution - non generisized	**106.28**	**106.224**	**102.8**	**93.4**	**95.062**	**89.83**	**86.81**	**88.438**	**80.6**	**81.804**	**77.522**	**76.41**	**106.44**

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

Time period	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	
Average evolution - generisized	**72.57**	**49.66**	**139.26**	**132.68**	**106.83**	**83.06**	**81.00**	**108.04**	**91.01**	**85.54**	**89.18**	**86.05**	
Average evolution - non generisized	**97.06**	**89.59**	**74.768**	**80.513**	**80.91**	**79.79**	**80.053**	**85.94**	**86.795**	**87.87**	**88.31**	**89.335**	

Annexure 7 Raw data on evolution indices and calculation of Pearsons correlation coefficient and coefficient of determination

Time period						
Average evolution - generisized						
Average evolution - non generisized						

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				Hypothesis testing		
				Sample size	**Sample mean**	**Sample variance**
				34	**86.64**	**16.7355**
				34	**97.40**	**17.2774**
				T statistic	**4.1252**	
					-10.77	
					-2.6098	