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Extent of Use and Compliance to Bisphosphonates in the Medical Management of Osteoporosis: An Observational Pilot Study in a Managed Care Organization

By

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Research Report

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In Pharmaceutical Affairs

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DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science at the University of the Witwatersrand. It has not been submitted before for any degree or examination in any other University or Technikon.

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_____ day of _____

ABSTRACT

The current study was a retrospective, observational pilot study designed to assess compliance to bisphosphonates treatment by patients diagnosed with osteoporosis (between 01 January 2010 and 17 August 2011). In this study, the cost of pharmacological agents used in the chronic medical management of osteoporosis was also estimated. The total number of patients whose records were eligible for analysis was 286, with the mean age of 66.7 years. The majority of patients' records (91%) were for females.

Alendronate was the most commonly used oral bisphosphonate with the utilization of the Osteobon® 70 mg/week generic formulation as high as 58.9%. Overall, the once-a-week bisphosphonate formulations were most preferred as evident from the utilization rate of 92.5%. Only 22.8% of patients were on Fosavance®. The overall treatment compliance was high at 74.1%. A proportion of 47.6% of patients using a combination of a bisphosphonate and proton pump inhibitors (PPIs) was also noted. In the absence of ICD-10 codes as an indicator for the use of PPIs, it was assumed that the PPIs were used to manage bisphosphonate-induced gastrointestinal adverse effects. This assumption is premised on the observation that bisphosphonates (chronic use) preceded the PPI use.

The total paid amount towards claims for bisphosphonates equalled R1 532, 642.54. Patients paid as high up to 40% of the claimed cost for chronic medication as levies. These costs are only for outpatient drug costs and do not factor costs for auxillary services and hospitalizations.

Understanding the complicated dosing instructions for the oral bisphosphonates, it is anticipate that adherence to the rigid dosing instructions may be a challenge for the elderly cohort. Should the latter hold true, it would thus be ideal to consider an endorsement of the use of a more convenient, once-yearly injectable bisphosphonate, viz 5mg zoledronic acid in the funder protocols. This formulation requires less frequent dosing, bypasses the GIT and is, more tolerable. In addition to the strength of the outcomes data on the reduction in fractures, the convenient dosing outweighs the use of cheaper options such as Osteobon® 70 mg/week, in terms of overall costs and compliance in osteoporosis management.

To my beloved daughter, Hikatekile Maluleke and my husband and dearest friend, Barhula Given H. Rikhotso

In loving memory of my father,
Mbazima Phineas "Fernandez" Maluleke
1955 – 1999

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Extent of Use and Compliance to Bisphosphonates in the Medical Management of Osteoporosis: An Observational Pilot Study in a Managed Care Organization

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University of the Witwatersrand in Johannesburg, 2013

Supervisors: Ms Princess Majola (external) and Dr. Neil Butkow (internal)

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ABBREVIATIONS AND ACRONYMS

BMD	-	Bone Mineral Density
FPP	-	Farnesyl Diphosphate Synthase
FRAX	-	Fracture Risk Assessment Tool
GIT	-	Gastrointestinal Tract
GP	-	General Practitioner
ICD-10	-	International Classification of Diseases Code 10
IV	-	Intravenous
MCC	-	Medicines Control Council
MIMS	-	Monthly Index of Medical Specialties
MPR	-	Medicines Possession Ratio
NOF	-	National Osteoporosis Foundation
ONJ	-	Osteonecrosis of the Jaw
OP	-	Osteoporosis
PBM	-	Pharmaceutical Benefit Manager
PMB	-	Prescribed Minimum Benefits
PPI	-	Proton Pump Inhibitor
SEP	-	Single Exit Price
VAT	-	Value Added Tax

CHAPTER ONE – OVERVIEW

1.1 INTRODUCTION

Osteoporosis is now recognized as a common and major public health problem. It was initially considered to be a condition that affects frail elderly women, as a natural part of aging. Although women past the menopausal stage are at a greater risk of being osteoporotic, osteoporosis is no longer considered an age- or sex-dependent disease. It can also affect men, across all age groups (including children) and different ethnic populations.

Osteoporotic fractures are associated with disabilities, immobilization, movement restriction, reduced quality of life as well as social isolation, increased risk of subsequent fracture, increased mortality, and high healthcare costs (Burge *et al,* 2007; Gabriel *et al*, 2002; Hallberg *et al*, 2004; Kanis *et al*, 2008; Bock and Felsenberg, 2008). Kanis *et al*, (1997) found that in women over the age of 45 years, osteoporosis accounts for more days in hospital than many other diseases, including diabetes, myocardial infarction and breast cancer.

The financial burden associated with osteoporosis-related fractures is estimated to range between US $14 billion (1995) (with hospital services accounting for 62%); to US $15 billion (2000) and US $17.5 billion (2002), annually in the USA (Pfister *et al,* 2006; Miller *et al*, 2005; McCombs *et al*, 2004). These estimates did not take into consideration the hospitalization costs (except the estimates for 1995), nor the impact of bone fragility and fractures on quality of life.

1.2 EPIDEMIOLOGY OF OSTEOPOROSIS

The prevalence of osteoporosis is currently estimated at over 200 million people worldwide (Delmas *et al*, 2007). As the prevalence of osteoporosis increases with age, it is estimated that by 2050, the worldwide incidence of hip fracture will increase by 240% in women and 310% in men (Bock and Felsenberg, 2008). The projected increase in the aging population may lead to an increase in the prevalence of osteoporosis (Burge *et al*, 2007).

Estimates of osteoporosis among perimenopausal and postmenopausal women range between 7 - 15% and 30 - 40%, respectively (Siris *et al,* 2001). In men aged >50 years, lower rates of 18 - 20% were reported (Siris *et al,* 2001). The prevalence of osteoporosis is estimated to be 7% in White men, 5% in Black men, and 3% in Hispanic men (Qaseem *et al,* 2008).

Osteoporosis often remains undetected and untreated until a fragility fracture occurs.

1.3 COMPLIANCE

Compliance is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen (Silverman, 2006). It also encompasses taking the medication as prescribed by the clinician with the given instructions such as taking medication after food not before or with food, with water and not milk. Poor compliance is a serious challenge in other asymptomatic chronic conditions such as diabetes, hyperlipidaemia and hypertension which require long term treatment (Reginister and Lecart, 2004; Gold *et al,* 2005; McCombs *et al,* 2004). Similarly, numerous studies have shown that the effectiveness of bisphosphonates in the treatment of osteoporosis is compromised by poor patient compliance. In addition, the high level of treatment compliance seen in randomized clinical trials cannot be reproduced in actual clinical practice.

Depending on the characteristics of the medication, the condition of disease and its severity; poor compliance can have serious consequences, which may include increased emergency room visits, hospitalizations and increased mortality (Gold *et al*, 2005).

Despite the documented serious consequences of poor compliance, it is reported that approximately 50% of patients fail to comply with osteoporosis therapy within the first year of treatment (Caro *et al,* 2004; Siris *et al,* 2006; Briesacher *et al,* 2007; Weycker *et al,* 2007; Rabenda *et al,* 2008).

In a study by Huybrechts *et al,* (2006) to assess compliance with osteoporosis treatment, a cohort of 38,120 women were enrolled. There was a rapid decrease in patient compliance during the first 2 years, after which compliance level became more stable at about 60%. Low compliance was associated with a higher risk of fractures regardless of other known important risk factors such as age, history of fractures, or prior osteoporosis medication (Huybrechts, *et al,* 2006). In addition, low compliance was found to be associated with higher hospitalization rates and higher charges for in- and out-patient health care resources (Huybrechts *et al,* 2006).

Similar observations were made on other studies. Solomon *et al,* (2005) in a study comprising of 40,002 patients with a mean age of 80 years, reported that 45.2% of patients discontinued osteoporosis treatment at the end of the first year, and 52.1% were not continuing to fill their prescriptions after 5 years. Patients who underwent baseline bone mass density (BMD) testing were found to be more likely to remain compliant with osteoporosis medications than those who did not undergo BMD testing during 12 months preceding medication initiation (Solomon *et al*, 2005). Furthermore, they found that compliance differed significantly with age, with the lowest compliance observed in patients 85 years and older.

Using a telephone survey, Silverman (2006) reported about a quarter (19% to 26%) of patients abandoned osteoporosis therapy within seven months. McCombs *et al,* (2004) found that 35 – 53% of osteoporotic patients beginning estrogen, bisphosphonate, or raloxifene therapy received less than three months of their initial therapy over the following one year period, 54 – 60% had six months or less. Keyser *et al,* (2001) reported the probabilities of therapy discontinuation over a two year period to be about 56% for women starting raloxifene, and 72% for those beginning treatment with estrogen. Recker *et al,* (2005), found that among women initiating daily and weekly bisphosphonate therapy, 87% and 75%, respectively, were adherent failure (adherence was defined as a medication possession ratio of 80% or greater during the one year follow up period).

As the dosing frequency was often cited as one of the major challenges, therapies with increased dosing frequencies were introduced in an attempt (in part) to improve patient compliance. Studies were conducted then to evaluate regimen preference between daily and weekly dosing, with the weekly regimen being preferred (Simon *et al*, 2002; Cramer *et al*, 2004; Recker *et al*, 2004; Kendler *et al*, 2004). However, even though patients using weekly bisphosphonate medication followed their prescribed dosing regimen better than those using daily therapy, overall compliance and persistence were found to be suboptimal (Cramer *et al*, 2007). In addition, in a study to compare the preference between the monthly ibandronate vs the weekly risedronate, more patients were found to prefer weekly risedronate over monthly ibandronate (82% vs 18% respectively) (Gold *et al*, 2006). Compliance was significantly higher in patients taking weekly risedronate vs monthly ibandronate (Gold *et al*, 2006).

1.4 MANAGEMENT OF OSTEOPOROSIS

The therapies available for osteoporosis management are conventionally classified as antiresorptive agents (they decrease bone resorption to produce secondary gains in bone mass) or anabolic agents (stimulate bone formation and increase bone mass) (Hough, 2005; Åkesson, 2003). These therapies range from over-the-counter supplements, such as calcium and vitamin D, to estrogen therapy, and bisphosphonates.

According to Brown *et al*, (2002) and Cummings *et al*, (1999) the primary goal of osteoporosis treatment is the prevention of vertebral and non-vertebral fractures. In patients with a history of fractures, the goal of treatment is to reduce vertebral and non-vertebral fractures. Treatment should target all aspects of the condition, namely: slowing down or stopping the mineral loss, increasing bone density, prevent bone fractures and minimize pain to those who already sustained a fracture. During menopause and the early postmenopausal period, efforts should be directed at preventing accelerated bone loss that occurs during this time (van Schoor, 2009). In men, aged 55 years and above, prevention of age-related bone loss is the goal. In women, it should be after the postmenopausal period. In the elderly population,

prevention of falls and fractures is an additional key goal, especially in those with a low bone mass (van Schoor, 2009).

1.4.1. CALCIUM AND VITAMIN D

Calcium and vitamin D are important nutrients in bone formation and maintaining healthy bone. These elements constitutes baseline treatment for osteoporosis and also used as a preventive measure, particularly in frail elderly patients (Åkesson, 2003). In most clinical trials, calcium and vitamin D are generally the baseline therapy. (NIH Consensus, 2001; Qaseem *et al*, 2008). Calcium is important for attaining peak bone mass; vitamin D is required for optimal calcium absorption. The recommended daily intake of calcium for an adult is 1 – 1.5g and 800 IU for vitamin D (Hough,2007).

1.4.2. HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) is approved for the prevention of fractures in early menopausal women and not indicated for the treatment of osteoporosis. HRT has been shown to reduce the occurrence of hip and vertebral fractures in clinical studies (Davis *et al*, 2010; NIH Consensus, 2001). Due to safety concerns following reports of increased risk of venous thromboembolic events, cerebrovascular accidents, breast cancer, and gynecological problems, HRT is to be used for a short period of time in women who are at a significant risk of osteoporosis (Davis *et al*, 2010; Åkesson, 2003).

1.4.3. SELECTIVE ESTROGEN-RECEPTOR MODULATORS

Raloxifene is a selective estrogen-receptor modulator (SERM) agonist in bone. It has been shown to reduce the risk of vertebral fractures in clinical studies (Hough, 2007; NIH Consensus, 2001). Raloxifene is indicated for osteoporosis in postmenopausal women with an added benefit of reducing the risk of breast cancer (Davis *et al*, 2010; NIH Consensus, 2001; Hough, 2007). However, raloxifene does not reduce the risk of hip fractures (Hough, 2007; Qaseem *et al*, 2008). The main adverse effects for raloxifene include hot flushes and venous thromboembolism (Hansberger, 2006).

1.4.4. CALCITONIN

Calcitonin is also an antiresorptive agent, indicated for the treatment of women who are at least 5 years postmenopausal. However, its effect on fractures has not been shown (Davis *et al*, 2010; Åkesson, 2003).

1.4.5. PARATHYROID HORMONE

Teriparatide is an anabolic agent, a recombinant for parathyroid hormone. It is used for the management of osteoporosis in postmenopausal women and in men with primary or hypogonadal osteoporosis who are at high risk for fracture. It is regarded as an alternative therapy for patients who cannot tolerate bisphosphonates (Davis *et al*, 2010). Long term safety effects of teriparatide have not been established. It is therefore recommended for use for up to 24 months (Hansberger, 2006). Adverse effects include hypercalcemia, hypercalciuria and the development of osteosarcoma.

1.4.6. BISPHOSPHONATES

Bisphosphonates are the standard of care for maintaining or increasing bone mass and reducing excessive bone turnover (Cole, 2010). In accordance with International Treatment Guidelines, bisphosphonates are recommended as first line agents in the treatment of osteoporosis (Adachi *et al,* 2007).

The new oral nitrogen-containing bisphosphonates (e.g. alendronate, risedronate, and ibandronate) act by inhibiting farnesyl diphosphate (FPP) synthase, a key branch point of the mevalonate pathway, and thus, inhibit protein prenylation in osteoclasts (Sunyecz, 2010).This pharmacodynamics property makes these bisphosphonates more potent in inhibiting bone resorption and remodelling (Sunyecz, 2010).

1.4.6.1. INDICATIONS FOR BISPHOSPHONATES

The Medicines Control Council (MCC)-approved indications for bisphosphonates, include: the prevention of fractures, treatment of osteoporosis and management of Paget's disease of the bone. Paget's disease is a chronic disorder that results in excessive breakdown and formation of the bone, causing fractures, skeletal abnormalities, and significant bone pain (MIMS 2010). Other approved indications

include heterotropic ossification, hypercalcaemia of malignancy, breast cancer, and multiple myeloma. Approved dosing by indications is listed in **Table 1**.

1.4.6.2. SAFETY AND TOLERABILITY

In general, the nitrogen-containing bisphosphonates have a good safety profile. Gastrointestinal adverse effect is the most commonly noted adverse effect. Other adverse effects include renal toxicity, influenza-like illness, osteonecrosis of the jaw, uveitis and atrial fibrillation (Fleisch, 2002; Kennel and Drake, 2009). Venous irritation and thrombophlebitis may be encountered with intravenous bisphosphonates, e.g. zoledronic acid 5mg (Bock and Felseberg, 2008; Sunyecz, 2010).

Table 1. **Bisphosphonates registered for Osteoporosis by the Medicines Control Council (MIMS, 2010)**

Active	Trade Name	INDICATIONS AS APPROVED BY THE MCC	Originator/Generic
ALENDRONATE	Fosamax®	Fracture risk reduction in postmenopause osteoporosis. Primary hypogonadotropin in men and vertebral fracture risk reduction	O
	Fosagen®	Postmenopausal osteoporosis in women	G
	Osteobon®	Osteoporosis in postmenopausal women. Glucocorticoid induced osteoporosis risk reduction /treatment in postmenopausal women not receiving oestrogen	G
	Ran-Alendronate®	Postmenopausal osteoporosis in women	G
	Sandoz Alendronate®	Postmenopausal osteoporosis in women	G
	Fosavance®	Postmenopausal osteoporosis in women and to help ensure Vitamin D is adequate	O
RISEDRONATE	Actonel®	Osteoporosis in postmenopausal women in combination with Ca 500-1000 mg/day and Vitamin D if deficiency suspected. Primary osteoporosis in males	O
ZOLEDRONIC ACID	Aclasta®	Osteoporosis in postmenopausal Reduce the incidence of new clinical fractures. Osteoporosis in men. Glucocorticoid induced osteoporosis	O

O - Originator

G - Generic

As a group, oral bisphosphonates are poorly absorbed from the gastrointestinal tract (less than 1%), are bone-selective, and lack systemic metabolism (Bock and Felsenberg, 2008). Absorption of bisphosphonates is nearly totally inhibited by food and beverages other than clear tap water. They should therefore be taken in the fasting state in an upright position, with water, at least 30 minutes before food intake (Recker *et al*, 2005; Kanis *et al*, 2008; Bock and Felsenberg, 2008; Reginister and Lecart, 2004).

Patients find these strict dosing instructions difficult to follow as they can be inconvenient and often not practical in the daily routine. Taking too little water or not staying upright for long enough after taking the dose, increases the risk of upper gastrointestinal adverse effects; failure to fast for a long enough period either before or after taking the bisphosphonate dose decreases absorption of the drug. This could potentially lead to insufficient reduction of the biochemical markers of bone turnover and sufficient BMD increases, resulting in an increased risk of fracture (Reginister and Lecart, 2004). These strict dosing instructions are cumbersome, especially for elderly patients with reduced cognitive function. Failure to follow these instructions may result in unwanted adverse effects (viz. gastrointestinal adverse effects) and reduced therapeutic outcomes of the bisphosphonate treatment.

Since these requirements cannot be altered, some patients are co-prescribed antacids to counter the bisphosphonates-induced gastrointestinal disturbances. Other adverse effects attributed to bisphosphonates use include: atrial fibrillation, myalgia, arthralgia and osteonecrosis of the jaw (ONJ). Factors that increase the risk of ONJ include: corticosteroid use, anticancer therapy, duration of bisphosphonate use, cigarette smoking, pre-existing dental disease, and intravenous bisphosphonates use (Davis *et al*, 2010).

1.5 MANAGEMNT OF BISPHOSPHONATE-INDUCED ADVERSE EFFECTS

The pharmacological management of gastrointestinal adverse effects include the use of acid-suppressive medications such as proton pump inhibitors, and histamine H_2 receptor antagonists. The use of these potent acid-suppressing agents for the treatment

of various disorders, ranging from gastroesophageal reflux to non-cardiac chest pain, continues to grow (Yu *et* al, 2008). The long-term effect of acid suppression include reduced calcium absorption, leading to decreased bone mass density (BMD) and increased incidence of osteoporosis (Adachi *et al*, 1998). In a study by Yu *et al* (2008), the use of acid-suppressive medications was found to be associated with modest increases in non-spine fracture risk in women, and also in men with low calcium intake. These findings suggest that PPIs may have unintended negative skeletal effects.

These findings support the speculation that the concomitant use of PPIs in osteoporosis management may have an antagonistic effect to bisphosphonates (Targownik *et al*, 2008; Madanick, 2011). The mechanism by which this antagonism occurs is not clear. It is thought that the inhibition of the production of intragastric secretion of hydrochloric acid (an important mediator of calcium absorption in the small intestine), induces calcium malabsorption (Vestergaard *et al*, 2006; Madanick, 2011). In other studies, it has been noted that the risk of fracture associated with PPI use is significant only in the presence of another risk factor (Madanick, 2011). This means that PPIs increase the risk in patients at high risk, confirming that they induce other changes in bone microstructure that increases the risk of fracture (Madanick, 2011). Since H_2 receptors are thought to be less effective than PPIs at promoting an acidic gastric environment (Yu *et al*, 2008), their use for gastrointestinal effects is not expected to be pronounced. As a result, they were not included in the current study.

1.6 AIM AND OBJECTIVES

The aim of the study was to establish the patterns of compliance to bisphosphonates treatment and related costs in the treatment of osteoporosis.

Amongst the many treatment options for osteoporosis, bisphosphonates were chosen to be the therapy of focus for this study. Reasons include the fact that they are the recommended first line agents and cornerstone therapy in osteoporosis treatment.

The main objectives of the study were to:

(i) quantitatively assess the levels of compliance to oral bisphosphonates,

(ii) quantify and assess the extent of use of agents used in the management of osteoporosis treatment-induced gastrointestinal adverse effects, and

(iii) estimate the cost of bisphosphonates utilized and other related medicines costs.

It is hypothesized that:

1. The real life data affirm that compliance to bisphosphonates when used for the osteoporosis indication is low, (Medicines Possession Ratio, MPR <80%).
2. Compliance levels are positively correlated to age (i.e. compliance is likely to improve with age).
3. In selected individuals who are at high risk of developing bisphosphonate-induced GIT adverse effects, concomitant use of bisphosphonates and proton pump inhibitors is high, although the latter is clinically counterproductive.

CHAPTER TWO – STUDY METHODOLOGY

2.1. STUDY DESIGN

This retrospective, observational analysis was designed to assess compliance to bisphosphonates in patients diagnosed with osteoporosis. Treatment records for bisphosphonates over a period of 19 months (from January 2010 to August 2011) were extracted. Claims for PPIs were also extracted (for patients on bisphosphonates).. .The extent of use of PPIs by patients chronically approved for bisphosphonates was also assessed. The ICD-10 codes (the International Statistical Classification of Disease and Related Health Problems 10th Revision) used for PPIs were not captured for all patients. The use of bisphosphonates and PPIs in patients with claims records for bisphosphonates was then used as a proxy for taking PPIs to treat bisphosphonates-induced gastrointestinal adverse effects. The starting time for PPI therapy in relation to bisphosphonate therapy was taken into consideration.

The cost of bisphosphonates used for osteoporosis was then derived from amounts claimed and paid for bisphosphonates.

2.2. STUDY POPULATION

The study population was drawn from the Provident Healthcare Risk Managers database. Providence Healthcare Risk Managers is an administrator and a pharmaceutical benefit manager (PBM) for a selected number of closed medical schemes, with a total of about 5,000 members. A majority of their clientele includes the miners. Providers contracted to Providence are reimbursed based on either a fee-for-service or through capitation model.

2.3. STUDY METHOD

A request for permission to access and use the database was sent to the manager of Provident Healthcare Risk Managers through a formal correspondence. An approval and permission was granted after reviewing the protocol proposal sent with the request. The healthcare database was transferred electronically and data was extracted, then formatted into a pivot table, and nested for bisphosphonates use, followed by PPI use.

A total of 286 patients with records for bisphosphonates use were isolated and included in the current study. Records were eligible for inclusion in the study if a patient had submitted a claim for an index prescription for bisphosphonate. Patients who were taking PPIs without treatment for osteoporosis were not included in the study. Patients who were on PPIs before starting therapy with bisphosphonates were excluded in any analysis related to co-treatment with PPIs.

Microsoft excel® (Windows 2010 package) was used to extract, filter and sort data for analysis. Bisphosphonate medication class (with a code 4.7.1.) was initially used to filter all bisphosphonate medications that were utilised during the January 2010 to August 2011 study period. Each bisphosphonate claim record was linked to the corresponding patient personal demographic details including age, gender, date of birth, unique identity (ID) numbers as well as information relating to transaction/doctor visits and frequency of medication dispensed. Patient ID numbers were used as unique identifiers to remove any duplicate entries. The total number of patients who were included in the study was 286. Fields contained in the data for analysis included:

- Brand, generic name and item code of the prescription dispensed (bisphosphonates and/or PPIs);
- the strength and quantity;
- date of prescription fill or refill;
- demographic information for each patient (date of birth, age and gender);
- amount paid for bisphosphonates and/or PPIs;
- amount claimed for bisphosphonates and/or PPIs;
- amount rejected for bisphosphonates and/or PPIs;
- amount levied type of service and type of professional rendering the service;
- type of referring doctor/prescriber/dispenser,
- type of institution where medications were dispensed (dispensing doctor, hospital or pharmacy).

Fields containing sensitive patient information (such as personal details, addresses, ID number and contact details), service providers names and addresses, medical aid name, medical aid plan and category of payment used, were excluded.

2.4. STUDY VARIABLES

2.4.1. COMPLIANCE

Compliance is the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen (Silverman, 2006). It is assessed by mean medication possession ratio (MPR). Compliance also encompasses taking the medication as prescribed by the clinician with the given instructions such as taking medication after food or before or with food, with water and not milk (Recker *et al*, 2005; Kanis *et al*, 2008; Bock and Felsenberg, 2008; Reginister and Lecart, 2004).

MPR is calculated by the frequency and length of script refill against the quantity dispensed, expressed as the ratio of cumulative number of days during which the patient had medication available divided by the length of follow up. (Siris *et al*, 2006). The number of refills between the date of first claim for bisphosphonate and the date of the last claim refill divided by days (in months) gave an indication of the compliance rate. During the 19 months study period, patients were classified as treatment compliant if their MPR was 0.80 or greater. Patients with an MPR less than 0.80 were classified as poor compliance. The MPR method of calculating compliance was used by Recker *et al* (2005), Silverman (2006) and Siris et al (2006), in their studies to determine adherence to bisphosphonate therapy and fracture rates in osteoporotic women.

2.4.2. TREATMENT COSTS

The acquisition costs for bisphosphonates and PPIs were acquired from the MIMS versions January 2010 and August 2011. The dates of these two versions of MIMS correspond with the dates of the study duration. The difference in Single Exit Prices (SEPs) was calculated and expressed as a percentage (**Table 2**). All prices included value added tax (VAT) at 14%. These prices were included to enable the comparison with the costs claimed and paid for by the scheme during the study period. They also highlight the differences in costs between bisphosphonates. As the once weekly and once daily regimens are sold in quantities that equals to a month's refill, the comparison of costs at this level was not carried out. The scheme liability towards chronic medication (bisphosphonates) was derived from the amount "paid" vs amount "claimed".

2.5. DATA ANALYSIS

The sample size required for statistical significance was 184. This sample size was estimated using the nQuery sample size calculator (equation:

$$N = \left[\frac{[z_{1-\alpha/s}\sqrt{\pi_{0(1-\pi_0)}}+Z_{1-\beta}\sqrt{\pi_1(1-\pi_1)}]}{(\pi 0-\pi 1)2} \right]^2$$ (Dixon and Massey, 1983).

N – required total sample size

Z – percentile of the standard normal distribution

π – proportions (the relationship between probability of events)

β – regression coefficient

s - variance

The data was analyzed using descriptive statistics, providing summary statistics which show means and frequencies. Compliance was calculated using the number of refills between the date of first claim for bisphosphonate and the date of the last claim refill divided by days (in months) expressed as a percentage i.e. Compliance % = (number of scripts collected/ length of follow up in months) x 100.. Proportions of compliance were compared between patients on bisphosphonates only and those on both bisphosphonates and PPIs using the two- sided test of hypothesis. Utilization rate for each bisphosphonate was also calculated using the number of refills across the study population divided by the total cumulative number of refills of all bisphosphonates, expressed as a percentage i.e. Utilization rate for bisphosphonate X % = (number of X scripts collected/ total number of all bisphosphonates' scripts collected) x 100. As the data were binomial, Pearson correlation and logistic regression analysis were used to assess the effect of age, copayment and concomitant PPI intake on compliance. . Level of statistical significance was $P<0.05$ (95% confidence interval). The software used included Microsoft Excel® and Stata 11 for the analysis of data.

2.6. ETHICS

To ensure patient confidentiality, all personal identifiers were removed from the database. The study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee on October 01, 2010 (Appendix I).

Table 2. **Single Exit Prices of the bisphosphonate therapies used in the current study by patients – Jan 01, 2010 to Aug 17, 2011**

Active	Trade Name	Strength (Quantity)	SEP January 2010	SEP August 2011	% Change
ALENDRONATE	Fosamax®	70 mg (x 4)	R 342.18	R 342.18	0%
		10 mg (x 30)	R 341.04	R 341.04	0%
	Fosagen®	70 mg (x 4)	R 216.85	R 205.75	**-5.12%** ↓
	Osteobon®	70 mg (x 4)	R 215.30	R 215.30	0%
		10 mg (x 30)	R 172.25	R 172.25	0%
	Ran-Alendronate®	70 mg (x 4)	R 190.15	Discontinued	-
	Sandoz Alendronate®	70 mg (x 4)	R 215.29	R 221.98	3.12% ↑
RISEDRONATE	Fosavance®	70 mg (x 4)	R 216.60	R 216.60	0%
	Actonel®	35 mg (x 4)	R 345.47	R 345.47	0%
ZOLEDRONIC ACID	Aclasta®	5 mg/5 ml (100 ml bottle)	R 3 187.38	R 3 423.26	7.4% ↑

CHAPTER THREE – STUDY RESULTS

3.1 BASELINE CHARACTERISTICS

The database consisted of 385 patients with claims for bisphosphonates. Bisphosphonate medication class was used as the primary entry criteria into the study since the use of ICD-10 code for osteoporosis was not consistent. Two hundred and eighty six patients met the inclusion criteria, implying that only 74.3% of the 385 patients diagnosed with osteoporosis were treated.

The mean patient age included in the cohort was 66.7 years (with a median age of 66 years), with approximately 54.5% of the patients above the age of 65 years, suggesting that studied cohort are elderly. Only 4.6% of the study cohort was under the age of 50 and 40.9% between the age of 50 and 64 years. Male patients accounted for 9.1% of the overall study population. See **Figure 1**

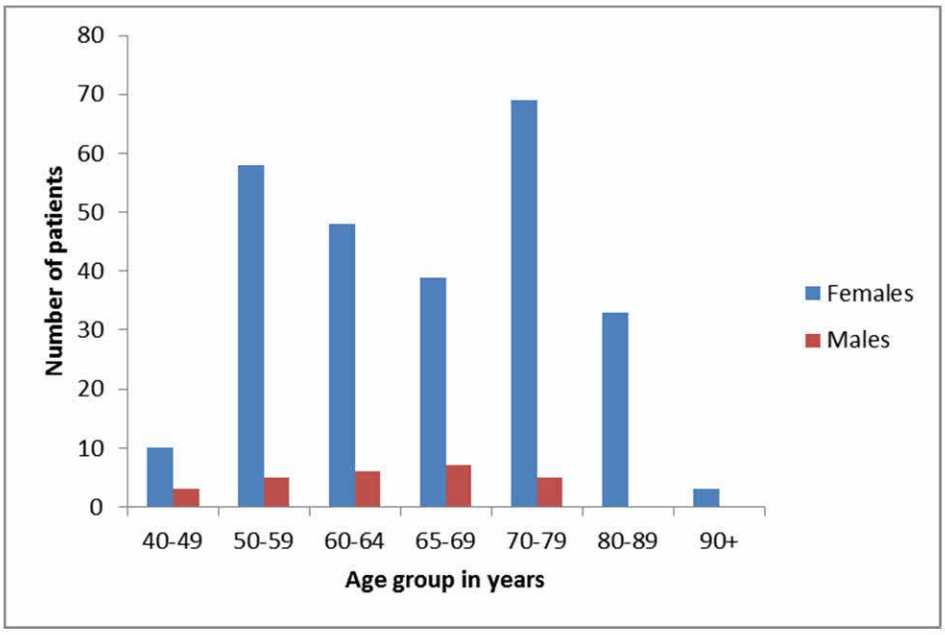

Figure 1. **Characteristics of the study patients**

3.2 STUDY MEDICATION AND CHOICE OF THERAPY

Two different generics of alendronate were used in this study cohort, namely: Fosagen® and Osteobon®. Although Fosavance® contains alendronate as an active

ingredient; it is a registered as a branded originator as it is formulated as a fixed dose combination of alendronate and cholecalciferol. Other branded original bisphosphonates included Fosamax®, Actonel® and Aclasta® for alendronate, risedronate and zoledronate, respectively. Analysis was therefore carried out with these generics as individual identifiable agents. Osteobon® 70 mg once-a-week regimen had the highest usage with a utilization rate of approximately 58.9% followed by Fosavance® at approximately 22.8% (**Figure 2**). The once-a-year regimen (Aclasta®) had a utilization rate of 0.8%. The once-a-week regimens made up 95.2% of the bisphosphonates utilized for the duration of the study period. Category "other" refers to other utilized drugs, not individually reflected (Fosamax 10 mg, Ran-Alendronate 70 mg, Sandoz Alendronate 70 mg and Zometa) had a low combined utilization rate of 1.7% (other). Other individually reflected drugs, Fosamax® 70 mg once-a-week, Actonel® 35 mg once-a-week, Fosagen® 70 mg once-a-week, and Osteobon® 10 mg once daily had a utilization rate of 5.2%, 4.8%, 3.1%, and 1.8% respectively.

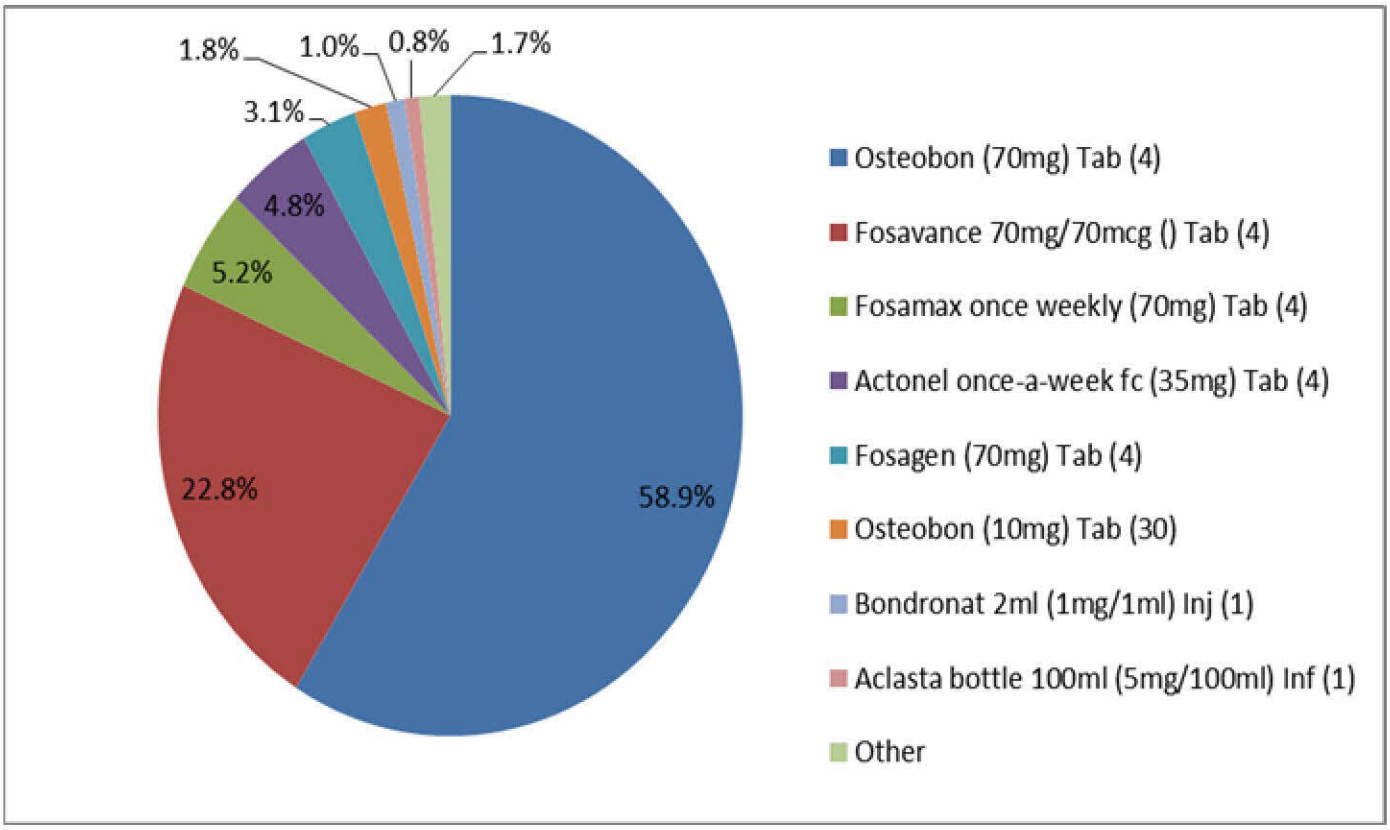

Figure 2 . **The rate of utilization of bisphosphonates over the 19 month study period**

Two patients in the study group received Zometa® and Bondronat® (actives are zoledronic acid and bandronic acid, respectively). While the ICD-10 code for these claims was for osteoporosis, the registered indications for these 2 agents are not osteoporosis. Despite the noted off-label use, these claims were paid by the scheme.

Within the study population, only 35 (12.2%) of the entire study's patients had their bisphosphonate medications switched. This could either suggest a good compliance to treatment or effective funder policy to drive adherence to protocol. Of those who switched, 7.3% (21) were to branded agents (**Table 3** and **Table 4**).

Table 3. **Therapeutic switches of bisphosphonates used in the treatment of osteoporosis between January 2010 and August 2011**

	Therapeutic (from - to)	Number of switches	Percentage of switch
Therapeutic	Alendronate generic 70mg - Risedronate 35 mg (Actonel®)	1	4.76%
	2x Alendronate generics 70mg + 1x Fosamax® - Zoledronate 5mg/100ml (Aclasta®)	3	14.29%
	Risedronate 35 mg (Actonel®) - Alendronate generics 70mg	3	14.29%
	Risedronate 35 mg (Actonel®) - Zoledronate 5mg/100ml (Aclasta®)	1	4.76%
	8x Alendronate generics 70mg + 3x Fosamax® - Alendronate + Cal 70mg (Fosavance®)	11	52.38%
	Alendronate + Cal 70mg (Fosavance®) - Alendronate generics 70mg	2	9.52%
	Total	**21**	

Table 4. **Generic switches of bisphosphonates used in the treatment of osteoporosis between January 2010 and August 2011**

	Generic (from - to)	Number of switches	Percentage of switch
Generic	6x Alendronate generics 70mg + 5x Fosamax® 70mg - Alendronate generics 70mg	11	78.86%
	Alendronate generics 70mg - Alendronate generics 70 mg	3	21.43%
	Total	**14**	

3.3 TREATMENT COSTS

3.3.1 BISPHOSPHONATES

The total amount, paid by the funder for bisphosphonates utilized, equalled R 1 532, 642.54 (on average, R5, 358.89 per patient). The cost of alendronate branded originator, Fosamax®, was estimated at R402.38 per patient per refill per month, while its generic Osteobon®, estimated to R258.02. The cost of Fosavance® estimated to R265.52 per patient per month. In addition, patients were paying a levy of approximately 14.5% of the payable amount on average (range 0.4% - 40%) with each refill. The difference between the SEPs and estimated refill cost per patient per month for Osteobon® and Fosavance®, (the only medicine with added cholecalciferol), are small, yet most patients were prescribed/taking Osteobon®.

3.3.2 PROTON PUMP INHIBITORS

Almost half of the patients (47.6%) within the pool used PPIs along with bisphosphonates; with the PPIs attributing to a total cost of R140, 927.92 (on average, R1, 036.23 per patient). The utilization rate of PPIs is summarized in **Figure 3**. It is apparent that omeprazole 20 mg is the predominant PPI. The majority of PPI treatment was dispensed on chronic basis. As little as 14.7% of the studied cohort received parenteral PPI formulations. It was assumed that the latter was administered in hospital. Accepting that PPIs can be switched to cheaper therapeutically equivalence alternatives, therapeutic switching between different PPIs occurred to some degree.

Table 5. **The estimated costs of bisphosphonates used for osteoporosis treatment between January 2010 and August 2011 per patient per refill.**

Active	Trade Name	Strength (Quantity)	Total Number of Claims	Bisphosphonates			
Cost of Medicines Utilized (South African Rands)				Claims Cost		Levy	
				Total Claimed	Cost/Pat/Refill	Total Charged	Average Cost/trans
ALENDRONATE	Fosamax®	70 mg (x 4)	174	R 70 013.66	R 402.38	R 5 403.09	R 31.05
		10 mg (x 30)	18	R 7 391.12	R 410.62	R 988.92	R 54.94
	Fosagen®	70 mg (x 4)	102	R 24 711.92	R 242.27	R 1 801.32	R 17.66
	Osteobon®	70 mg (x 4)	1964	R 506 751.93	R 258.02	R 21 349.57	R 10.87
		10 mg (x 30)	59	R 12 546.46	R 212.65	R 340.03	R 5.76
	Ran-Alendronate®	70 mg (x 4)	19	R 1 585.45	R 176.16	R 182.30	R 20.26
	Sandoz Alendronate®	70 mg (x 4)	3	R 797.01	R 265.67	R 114.35	R 38.12
	Fosavance®	70 mg (x 4)	761	R 202 057.56	R 265.52	R 11 133.34	R 14.63
RISEDRONATE	Actonel®	35 mg (x 4)	137	R 66 857.72	R 488.01	R 7 069.58	R 51.60
ZOLEDRONIC ACID	Aclasta®	5 mg/5 ml (100 ml bottle)	27	R 93 184.86	R 3 451.29	R 4 423.98	R 163.85

Pat - patient

Trans - transaction

Levy – the amount paid by the patient (difference between the amount paid by the scheme and that claimed by the service provider)

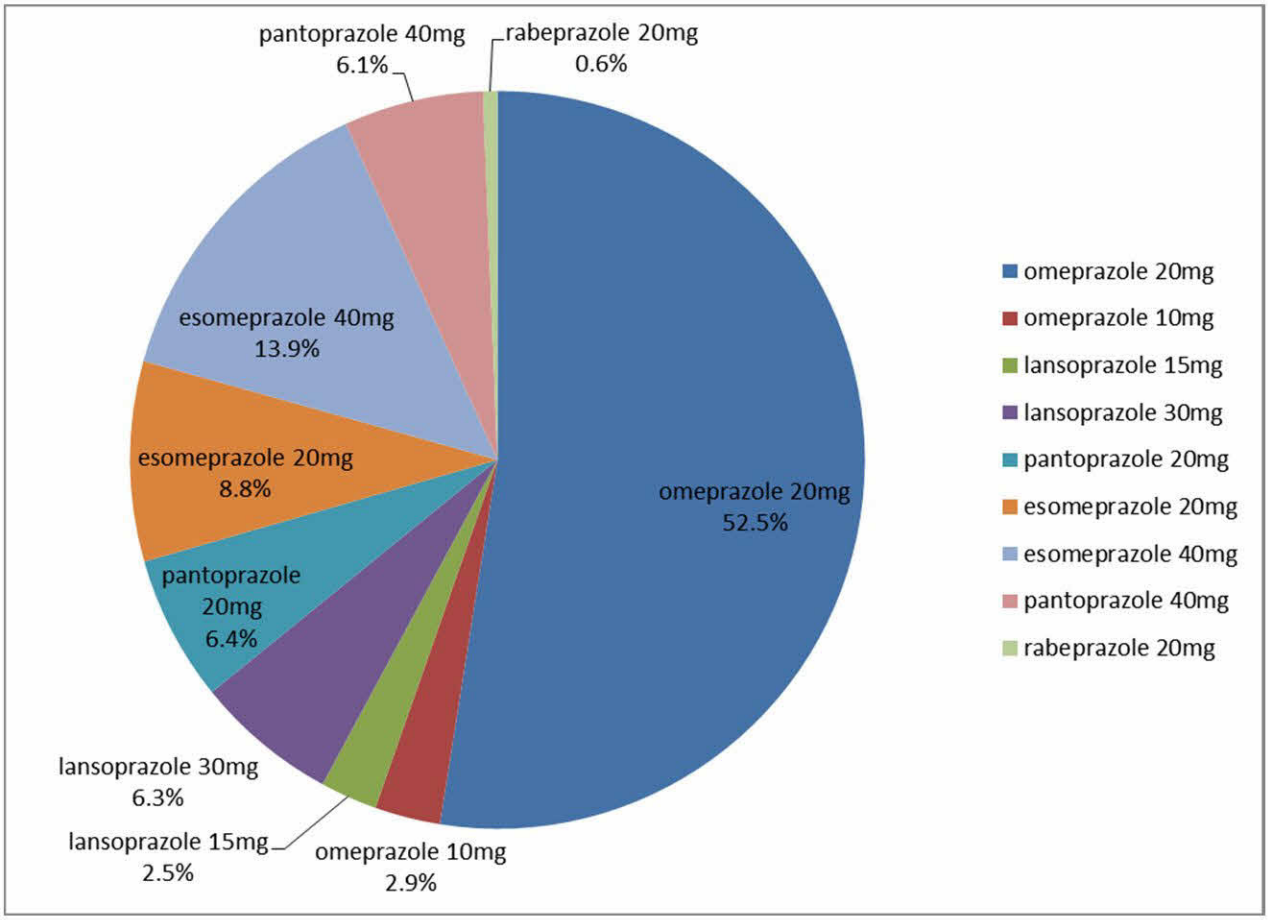

Figure 3. **The rate of utilization for proton pump inhibitors according to the active moiety**

3.4 COMPLIANCE

Compliance was computed by assessing the number of dispensary transactions for bisphosphonates over the 19 month study period. The quantity of medication filled/refilled and the time of the month of filling/refilling was taken into consideration.

Overall compliance was relatively good, with 74.1% of the patients in the study achieving an MPR >80%. Compliance was higher in elderly patients. Switching did not seem to have adversely affected patient compliance to treatment. Only 14.3% (5) of the patients who switched their medication had a low compliance rate, with an MPR <80%

3.5 CORRELATION ANALYSIS

3.5.1. Compliance versus Age and Gender

Using Pearson correlation (correlation coefficient = 0.042) between age and compliance percentage score by age, gender, elderly female (≥65 years) had a higher compliance level of 78.2% ± 3.6 as compared with 70.1% ± 4.1 for patients younger than 65. Amongst the male patients, the level of compliance in the elderly patients was higher compared to those younger than 65 years (91.7% ± 8.3 versus 57.1% ± 1.4, respectively). Refer to statistical output below (Error! Reference source not found. and **Table 7)**.

Table 6. **Proportions of level of compliance in female patients only (n = 260)**

Compliance(F)	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
Non compliant				
<65	29.9	4.1	21.9	38.0
≥65	21.8	3.6	14.7	28.9
Compliant				
<65	70.1	4.1	62.0	78.1
≥65	78.2	3.6	71.1	85.3

Table 7. **Proportions of level of compliance in male patients only (n = 26)**

Compliance(M)	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
Non compliant				
<65	42.9	13.7	14.6	7.1
≥65	8.3	8.3	8.8	25.5
Compliant				
<65	57.1	13.7	28.9	85.4
≥65	91.7	8.3	74.5	108

When grouped according to age only, compliance was 79.3% ± 3.4 higher in elderly patients above 65 years of age in comparison to patients less than 65 years old, with a compliance level of 68.8% ± 3.9 (

Table 8). There seem to be an association between age and compliance.

Table 8. **Proportions of level of compliance over age (n = 286)**

Compliance	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
Non compliant|				
<65	31.2	3.9	23.5	38.9
≥65	20.7	3.4	14.0	27.3
Compliant |				
<65	68.8	3.9	61.1	76.5
≥65	79.3	3.4	72.7	86.0

When assessing compliance between females and males with no regard to age, there was no difference in the level of compliance (74.2% ± 2.7 and 73.1 ± 8.9% respectively) (**Table 9**). Thus compliance was not driven by gender.

Table 9. **Level of compliance over gender (n = 286)**

Compliance	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
Non compliant|				
Female	25.8	2.7	20.4	31.1
Male	26.9	8.9	9.5	44.4
Compliant |				
Female	74.2	2.7	68.9	79.6
Male	73.1	8.9	55.6	90.5

Using a logistic regression analysis, there is a significant difference in compliance levels between the elderly (≥ 65 years) and those less than 65 years, with a 1.74 greater probability of elderly patients being compliant (p < 0.05) (**Table 10**). The declining cognitive ability and possible concomitant chronic medications for other conditions, does not seem to have a negative impact on compliance to osteoporosis treatment in these elderly patients. Patients below the age of 65 years were 1.27 less likely to comply with their osteoporosis treatment.

Table 10. **Logistic regression of compliance by age group (n = 286)**

Compliance|	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age >65	1.738832	.4764067	2.02	0.043	1.016353	2.974887
<65	1.267831	.5291206	0.57	0.570	.5595237	2.872794

3.5.2. Compliance versus Concomitant Proton Pump Inhibitor use

There were 49.2% ± 3.1 of females taking bisphosphonates with PPIs as compared to 34.6% ±9.5 of males (**Table 11**). The high proportion of females on concomitant PPI could have been due to the high ratio of females included in the study to males (approximately 10:1). It could also be due to women being more knowledgeable and aware of their condition and treatment options.

Table 11. **Proportion of level of Proton Pump Inhibitor use over gender (n = 286)**

PPI Use	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
No PPI				
Female	50.8	3.1	44.7	56.9
Male	65.4	9.5	46.7	84.1
PPI_Use				
Female	49.2	3.1	43.1	55.3
Male	34.6	9.5	15.9	53.3

The concomitant use of bisphosphonates and PPIs was slightly higher in elderly patients with 51.0% ± 4.2 PPI utilization rate and 44.7% ± 4.2 in patients less than 65 years old (**Table 12**). These proportions indicate that the use of PPIs is not influenced by age.

Table 12. **Proportion of level of Proton Pump Inhibitor use over age group (n = 286)**

PPI Use	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
No PPI				
<65	55.3	4.2	47.0	63.6
≥65	49.0	4.2	40.8	57.2
PPI_Use				
<65	44.7	4.2	36.4	53.0
≥65	51.0	4.2	42.8	59.2

When a separate analysis of compliance according to age and concomitant PPI use was carried out within each gender, elderly female patients had a slightly higher compliance rate of 51.9% ± 4.3 as compared to 46.5% ± 4.4 in patients less than 65 years old (**Table 13**). Again, age seem to have a positive influence on compliance.

Table 13. **Level of compliance over Proton Pump Inhibitor use and age group in female patients only (n = 260)**

Compliance (F)	Proportion (%)	Std. Err. (%)	[95% Conf.	Interval]
No PPI				
<65	53.5	4.4	44.8	62.3
≥65	48.1	4.3	39.6	56.7
PPI_Use				
<65	46.5	4.4	37.7	55.2
≥65	51.9	4.3	43.3	60.4

The compliance level in their male counterparts was lower, with 41.7% ± 14.9 in elderly patients and 28.6% ± 12.5 in patients less than 65 years (Table **14**).

Table 14. **Level of compliance over Proton Pump Inhibitor use and age group in male patients only (n = 26)**

Compliance (M)	Proportion (%)	Std. Err. (%)	[95% Conf.	Interval]
No PPI				
<65	71.4	12.5	45.6	97.2
≥65	58.3	14.9	27.7	88.9
PPI_Use				
<65	28.6	12.5	2.8	54.4
≥65	41.7	14.9	11.1	72.3

In the overall analysis, patients who were also taking PPIs had a 39% ± 1.68 less probability of compliance when compared to patients who were taking bisphosphonates only. There was however, no significant difference observed ($p < 0.05$) (Table **15**).

Table 15. **Logistic regression of compliance over Proton Pump Inhibitor use (n = 286)**

Compliance	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
PPI Use	.6186406	.1684394	-1.76	0.078	.3628096	1.054868
No PPI	3.65625	.7293922	6.50	0.000	2.473023	5.405597

3.5.3. Compliance versus Co-payment and gender

Co-payment was higher in females than in male patients (40.4% ± 3.0 versus 26.9% ± 8.9, respectively) (**Table 16**). This could be as a result of disproportion ratio between male and female patients included in the study.

Table 16. **Proportion of level of co-payment by gender (n = 286)**

Co-Payment	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
No co payment|				
Female	59.6	3.0	53.6	65.6
Male	73.1	8.9	55.6	90.5
Co-payment |				
Female	40.4	3.0	34.4	46.4
Male	26.9	8.9	9.5	44.4

When stratified according to age group, there was no difference in co-payments between the elderly and patients less than 65 years (39.3% ± 4.1 versus 39.0% ± 4.1) (**Table 17**). Co-payment was not influenced by gender. As elderly patients are more likely to be on cheaper options of the medical insurance due to affordability, this may imply that their cover option does not have an impact on co-payment.

Table 17. **Proportion of level of co-payment by age group (n = 286)**

Co-payment	Proportion(%)	Std. Err.(%)	[95% Conf.	Interval]
No co-payment|				
<65	61.0	4.1	52.9	69.1
≥65	60.7	4.1	52.7	68.7
Co-payment |				
<65	39.0	4.1	30.9	47.1
≥65	39.3	4.1	31.3	47.3

When grouped according to age within each gender, there was no difference in the level of compliance between the elderly with co-payments and those less than 65 years of age in female patients (39.8% ± 4.3 and 40.9% ± 4.4, respectively; $p < 0.05$) (**Table 18**).

Table 18. **Proportion of level of compliance over co-payment and age in female patients only (n = 260)**

Compliance (F)	Proportion (%)	Std. Err. (%)	[95% Conf.	Interval]
No co-payment				
<65	59.1	4.4	50.4	67.7
≥65	60.2	4.3	51.8	68.5
Co-Payment				
<65	40.9	4.4	32.3	49.6
≥65	39.8	4.3	31.5	48.2

Compliance level was 33.3% ± 14.2 in elderly male patients above the age of 65 years and 21.4% ± 11.4 in male patients below the age of 65 years, both age groups with co-payments (**Table 19**). The very low compliance levels in these patients indicate that the concomitant use of PPIs did not improve adherence to treatment.

Table 19. **Proportion of level of compliance over co-payment in male patients only (n = 26)**

Co-payment (M)	Proportion (%)	Std. Err. (%)	[95% Conf.	Interval]
No copayment				
<65	78.6	11.4	55.1	102.0
≥65	66.7	14.2	37.4	95.9
Co-payment				
<65	21.4	11.4	2.0	44.9
≥65	33.3	14.2	4.1	62.6

Regardless of the age and gender, patients with co-payments had a 1.6 times greater odd of being compliant as compared to patients without co-payments. However, there was no statistical significant difference observed in the level of compliance between the two groups ($p < 0.05$) (**Table 20**).

Table 20. **Logistic regression of compliance over co-payment (n = 286)**

Compliance	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Co-Payment	1.604454	.4607106	1.65	0.100	.913922	2.816731
No co-payment	2.411765	.4016723	5.29	0.000	1.740082	3.34272

When assessing compliance against all parameters together, age showed significance in the level of compliance (OR 1.81, CI 95%) (**Table 21**). Elderly patients

(above 65 years) were twice as likely to be compliant as compared to those below the age of 65 years, keeping all other factors fixed. Similarly, patients who were concomitantly taking PPIs show less compliance in comparison to those taking bisphosphonates only. This was found to be marginally significant (p = 0.068, when using the real life significance level of 10%). Co-payment did not have much effect on compliance (**Table 21**).

Table 21. **Logistic regression of overall factors (n = 286)**

Overall	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Co-Payment	1.571379	.4571138	1.55	0.120	.8885184	2.779043
age	1.810405	.5032146	2.14	0.033	1.049974	3.12157
PPI Use	.6036961	.1671974	-1.82	0.068	.3508107	1.038877

When assessing compliance against all parameters together within each gender, the data for male patients was too scanty to produce any reliable data (**Table 22**).

Table 22. **Logistic regression for all factors in male patients only (n = 26)**

Overall (M)	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Co-Payment	1	(omitted)				
age	9.157085	11.47913	1.77	0.077	.7847088	106.8577
PPI Use	1.744016	2.011092	0.48	0.630	.1819689	16.71489

Amongst the female patients, results indicated that the concomitant use of PPIs had a significant difference in the level of compliance instead of the age as indicated in the overall analysis above (p < 0.05) (**Table 23**). Concomitant PPI intake in these patients had a positive impact on their compliance to a certain degree.

Table 23. **Logistic regression of all factors in female patients only (n = 260)**

Overall (F)	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Co-Payment	1.368841	.4102603	1.05	0.295	.7607402	2.46303
age	1.598462	.4630211	1.62	0.105	.9060193	2.820116
PPI Use	.5597863	.1631175	-1.99	0.046	.3162194	.9909596

From below (**Table 24**), it is clear that there is an association between the level of compliance and age, with 79% of patients above 65 years old being compliant as compared to 68.8% of patients below the age of 65 years old.

Table 24. **Chi Square table showing association between compliance and age (n = 286)**

Compliance	<65	≥65	Total
Not Compliant	44	30	74
	59.46	40.54	100.00
	31.21	20.69	25.87
Compliant	97	115	212
	45.75	54.25	100.00
	68.79	79.31	74.13
Total	141	145	286
	49.30	50.70	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 4.1218 Pr = 0.042
Fisher's exact = 0.044

There is an association between compliance and gender (Fisher's exact test = 0.044)

Keys:

Std Err – standard error

95% conf. interval – 95% confidence interval

F – females

p – probability

z – percentile of standard normal distribution

M - males

CHAPTER FOUR – DISCUSSION

The majority of patients included in the current study were elderly (54.5%), with an average age of 66.7 years (**Figure 1**). Men constituted only 4.2% of this elderly group, and 9.1% of the entire study population. This may indicate either that men are still under diagnosed, under treated or that their risk of suffering from osteoporosis is not as high as the risk for postmenopausal women. Juby and Davis (2001) conducted a study to evaluate the awareness, knowledge, risk factors and current treatment of osteoporosis in elderly patients. The study included 39 men and 106 women, with an average age of 76 years. Men were found to be less aware and knowledgeable about osteoporosis than women ($p < 0.01$, and $p < 0.05$; 95% CI). Furthermore, 50% of women were taking calcium supplements compared with 15% men ($p < 0.001$; 95% CI), which is an indication of a high level of awareness of osteoporosis in this cohort of patients.

Reported compliance rates are consistently low in the osteoporosis literature (Cramer, 1995; Solomon *et al*, 2005; Cole, 2010; Dugard *et al*, 2010; Caro *et al*, 2004). Noncompliance seems to be a serious concern across the board regardless of the underlying disease, symptoms, treatment regimen or patient's age, with between 40–50% of patients failing to continue treatment beyond 12 months (Saambrook, 2006). In contrast to these findings, compliance rate in the current study was good, with 74.1% patients achieving an MPR>80% during the 19 months study period. Furthermore, a higher level of compliance was observed in elderly patients (79.3%) compared to patients below the age of 65 years (68.8%).

While some studies have cited that compliance declines rapidly within the first 12 months to two years, (Huybrechts *et al*, 2006; Saambrook, 2006; Solomon *et al*, 2005), it is unlikely that the compliance level could have dropped within the balance of the five months (to make 24 months). In addition, the patients who achieve one year of uninterrupted medicine therapy for osteoporosis are believed to achieve better patient outcomes than those who terminate or interrupt therapy during the first year (McCombs *et al*, 2004). These better outcomes could also serve as a motivation for the compliant patients to further comply with their treatment regimens. In general, there is a low

percentage of patients (less than 25%) who achieve in excess of one year without breaking therapy and approximately 30% of patients who switch therapies (McCombs *et al*, 2004).

Osteobon®, was the preferred agent. This could be due to a number of reasons, including generic substitution, low cost and protocol inclusion- implying full cover by the scheme without any co-payment. Since osteoporosis is best managed by taking calcium and vitamin D supplements in addition to osteoporosis treatment; it is unclear why only a relatively small percentage of patients (22.8%) were on Fosavance®. This low utilization of Fosavance® suggests little appreciation of the value of calcium in osteoporosis treatment. As oral bisphosphonates have the same pharmacokinetic properties and adverse effects profile, it is unclear what drove the choice of bisphosphonate regimen most commonly used (Osteobon®). Further questioning relating to affordability, protocol or prescribing behaviour Is warranted in answering this question. There is also a possibility that patients may have been purchasing their own calcium supplements over-the-counter. As this information was not reflected in the database used, this speculation could not be verified.

Given the prevalence of vitamin D deficiency in the elderly, ensuring adequate intake of nutrients both before and after initiation of bisphosphonate therapy is an important but frequently overlooked aspect of providing optimal care of skeletal health (Kennel and Drake, 2009). 800 IU of vitamin D in combination with calcium would be an ideal supplement for patients with osteoporotic fracture risk (Brown and Jose, 2002). In addition, efficacy of osteoporosis medication has generally been studied concomitantly with calcium or calcium and vitamin D. These supplements should thus be used in combination with osteoporosis medicines (van Schoor, 2009). As such, it is not clear why Fosavance® was not the treatment regimen of choice or why clinical practice does not encourage the use of Fosavance®. The use of Fosavance® would reduce the pill burden and subsequently reduce the overall cost of osteoporosis management since the acquisition price of Fosavance® and Osteobon® is nearly the same (**Table 5**).

The extracted database used did not contain information on the use of over-the-counter medications, it was therefore not feasible to trace and assess the extent of use of calcium and vitamin D supplements.

It was observed that 35 (12.2%) patients switched their treatment regimens during the 19 month study period. The switch rate was low; especially when compared to the 30% in McCombs *et al* (2004), with only 7.3% of the patients switching therapeutically (**Table 3**). Generic switching was only 4.9% (**Table 4**). Within the therapeutics switches, the majority of switching were to Fosavance® (3.8%), which could have been as a result of patients/prescribers realising the additional benefits of this regimen, at nearly the same cost as the most commonly used Osteobon®. It was also noted that there were switches between the generic agents to some degree. It is not clear what motivated the need for switches within the generic agents as it is unlikely to be due to tolerance and/or affordability.

Bisphosphonates have a similar safety profile and generics are generally within the same price range. The introduction of once-a-week formulations into the market was as an acknowledgement of the challenges presented by the once-daily dosing/requirements. Understandably, the switches to Osteobon® could be protocol driven as most patients were already on this therapy. On the other hand, the switch from Osteobon® 10 mg once-a-day regimen to Osteobon® 70 mg once-a-week may be mainly driven by convenience. Compliance for patients taking Osteobon® 10 mg once-a-day was very low and the switch by the 3 patients to once-a-week regimen is commended, with a hope that compliance would improve.

It has been documented that patients on bisphosphonates often take potent PPIs, to counter the bisphosphonates-induced gastrointestinal adverse effects. It is therefore expected that patients on concomitant treatment with bisphosphonates and PPIs would have an improved compliance. Concomitant use of PPIs was slightly higher in elderly patients (51.0% ± 4.2) compared to patients below the age of 65 years (44.7% ± 4.2) (**Table 12**). A slightly higher compliance level of 51.9% ± 4.3 was observed in elderly patients when looking at the female subgroup only (**Table 13**). Although lower than the

female subgroup, elderly males also had a slightly higher compliance level than those below the age of 65 years (41.7% ±14.9 versus 28.6% ± 12.5, respectively) (**Table 14**). In contrast to the expectation for an improved compliance in these patients (taking bisphosphonates and PPIs concomitantly), a 39% less probability of compliance was detected (**Table 15**). However, there was no statistical significant difference observed in the compliance levels of patients on bisphosphonates only and the 47.6% patients on both bisphosphonates and PPIs ($p < 0.05$) (**Table 15**). This implies that concomitant intake of PPIs does not necessarily help improve compliance to bisphosphonates therapy.

The other factor which could have influenced compliance is co-payment. Some patients were subjected to paying a levy that ranged from 0.4% to 40% of the claimed amount. Considering that the studied population consisted predominantly of elderly patients, it is safe to assume that in addition to osteoporosis, they also have other co-morbidities. With this in mind, they were obviously subjected to co-payments for other concurrently occurring diseases. Reasons for patients to pay such high levies are not clear but could be in partly due to the funding rules and may include any of the following, depending on the level of cover and/or medical aid option:

- penalty for out of formulary drug choice/use.
- penalty for use of out of designated service provider dispensary/pharmacy.
- low reference price, relative to the cost of prescribed medication.
- exceeding the limited chronic benefit for osteoporosis.
- high dispensing fees chargeable at the point of medication dispensary

Approximately 40.4% ± 3.0 of females were subjected to paying the levy as compared to 26.9% ± 8.9 of males (**Table 16**). Compliance level was slightly higher in elderly male patient (33.3% ± 14.2) and only 21.4% ± 11.4 in patients below the age of 65 years (**Table 19**). This implies that paying of levies influenced compliance to a certain extent in elderly male patients. However, there was no correlation between co-payment and compliance in the overall analysis. The slight influence observed amongst the elderly male patients was therefore marginal.

It was not possible to analyse the impact on fractures. Only data on chronic ambulatory outpatient medical care was available. One may predict that in patients on concomitant bisphosphonates and PPIs, the risk of fracture would increase. The literature suggests that a combination of PPIs and bisphosphonates has an antagonistic effect on bone protection (Targownik *et al*, 2008; Madanick, 2011). PPIs affect bone mineral metabolism. They act by inhibiting the production and intragastric secretion of hydrochloric acid, which is believed to be an important mediator of calcium absorption in the small intestine (Targownik *et al*, 2008). The risk of fracture associated with PPI use is reported to only increase in the presence of another risk factor (Madanick, 2011).

The cost of osteoporosis management is not only attributable to drug cost, but also includes indirect costs associated with the disease. These indirect costs are estimated to account for at least 20% of the total costs of treatment (Lindsay *et al*, 2001). Indirect costs could include services such as co-prescriptions, radiology tests for different fractured areas (i.e. wrist, hip, limb, spine), emergency rooms' services, hospitalizations and long periods of rehabilitation usually associated with an osteoporotic fracture. Furthermore, these estimates ignore the effect of bone fragility and fractures on quality of life. Health related quality of life and survival are substantially reduced after experiencing an osteoporotic fracture (Boonen *et al*, 2009).

Rabenda *et al*, (2006) reported that medical examination accounted for the largest component of costs (42.5%) in the Belgian population, whereas visits to health professionals accounted for 24.7%. This was estimated to a substantial total of direct disease-related costs of approximately €44.6 per osteoporosis patient per month, which is extrapolated to € 145 per patient per year (Rabenda *et al*, 2006).

As the cost of medication is also believed to influence compliance, some patients may not be able to afford treatment, particularly where co-payments are high (Gold and Silverman, 2005). It is reported that approximately 11% of hospital admissions of elderly patients is related to poor compliance, while more than 0.5 million hospital admissions annually can be attributed to inappropriate use of medications (e.g. not taking enough

medication, wrong dosing, dosing erratically) (Cramer, 1995). In a study conducted in Israel, it was found that the number of women on osteoporosis medication and persistence with therapy increased when co-payments were eliminated for osteoporosis medications specifically (Gold and Silverman, 2005). However, having a good medical aid insurance does not necessarily guarantee that people with a chronic, asymptomatic disease will take their medications over the long term (Gold and Silverman, 2005). Secondly, these kinds of outcomes are only achieved in randomized clinical trials where there is strict selection of study participants and the tightly controlled design, which is difficult to apply in real life clinical practice such as observed in this study. Patients in the current study had considerably high co-payments, i.e. up to 40% of medication cost. This could have a negative effect in patients' compliance and adherence in the long term.

Elderly patients who are likely to be on pension, are more likely to opt for low level, cheap options, with high insurance levels for selected disease conditions. . Adding to the constraint would be the strict dosing requirements, such as to remain upright and to take the medication on an empty stomach, as this patient group is unlikely to comply with all of these strict dosing instructions and the resulting inconvenience.

Thus, it can be concluded that the availability of a less frequently dosed agent, more tolerable, affordable and similarly effective drugs would address and meet the needs of most osteoporosis patients, particularly the elderly. Weekly and monthly regimens are convenient and associated with better compliance and treatment persistence compared to the daily regimens. As an alternative, the use of Fosavance® would, at least reduce the costs of supplements as well as reduce the overall pill burden. However, it will not address the bisphosphonates-induced GIT adverse effects.

Despite the noted benefits, weekly dosing regimens have not been shown to improve adherence to appreciably higher levels (Weis *et al,* 2007; Cramer *et al,* 2007; Cooper *et al,* 2006). As Cramer (1995) stated "patients may not normally take all medication as prescribed, making it impossible to establish general guidelines on what to expect when using specific medications". An ideal solution to ensure compliance is

the use of a single annual injectable formulation (Cramer, 1995). Clinical data from trials demonstrated that Aclasta® produced mean increases in BMD 1 year later of 4.6% and 3.3% (both $p<0.001$)) for lumbar spine and hip region, respectively. (Reid *et al*, 2002). In addition, Brown *et al*, (2007) found no serious drug-related adverse effects associated with prolonged use of single dose zoledronic acid (5mg), including renal toxicity or reported osteonecrosis of the jaw.

Moreover, the use of intravenous (IV) Aclasta® would bypass the gastrointestinal tract and thereby avoid the complicated, inconvenience dosing instructions for oral bisphosphonates that many patients end up disregarding. Since IV administration occurs under medical supervision, patients are monitored for any untoward effects following injection. Bock and Felsenberg (2008) have indicated that adverse effects on renal functioning with dosages used for postmenopausal osteoporosis are generally rare and primarily related to infusion rate and dose. Additionally, the nitrogen-containing IV bisphosphonates (ibandronate and zoledronic acid) have shown a better safety profile in relation to renal toxicity (Chang *et al*, 2003; Delmas *et al*, 2006; Black *et al*, 2007; Lyles *et al*, 2007) as compared with earlier bisphosphonates (etidronate, clodronate).

CHAPTER FIVE - LIMITATIONS TO THE STUDY DESIGN AND CONCLUSION

Clinical and claims databases have been widely used to evaluate the impact of adherence to various osteoporosis therapies on clinical, health care utilization, and cost outcomes (Caro *et al*, 2004; Recker *et al*, 2005). These observational retrospective designs permit evaluation of a much larger and potentially greater representative sample of patients than is possible in a randomized control study, in particular, the retail pharmacy database, as the claims database may under-represent lower-income patients who do not have medical aid insurance.

Medical and pharmacy claims data report only prescription filling, not actual medication use. The following are limitations associated with using medical and pharmacy claims databases (Huybrechts *et al*, 2006; Solomon *et al*, 2005; Silverman, 2006):

- Some of the observed gaps in medication availability may be due to temporary loss of insurance coverage which could lead to an overestimation of the level of non-compliance if patients obtain or take their medications regardless.
- The monthly charges may be somewhat underestimated because some physicians or medical institutions have a capitation agreement with the insurance provider whereby they receive a fixed amount per patient and not charge for each consultation or service. Details of such transactions are generally not captured nor reflected in the schemes records.
- Inability to assess the reasons for starting or stopping medications
- Non-compliance with other medications may have been at the advice of physician on the basis of potential risks and/or adverse effects.
- Patients who change level of cover of insurance Administrative claims are an indirect measure of medication-taking behavior, the availability of a prescription claim does not necessarily imply that the patient took the medication effectively.
- Age group bias toward the elderly. It cannot be predicted whether a similar trend would apply if the age demographics were different.
- The H_2 antagonists were not included for analysis in the study, as these were mostly acute claims.

- Information is limited to one database covering one private sector. These results cannot be extrapolated to cover patients in the public sector in which the majority of the patients may fall.

CONCLUSION

Despite the fact that non-experimental studies such as the one presented here cannot by themselves establish causality, they are an important link in the chain of evidence that poor compliance leads to an increase in the utilization of health care resources. The management of osteoporosis and related fractures is very costly as it involves utilization of expensive resources such as specialists (orthopaedics, radiologists etc.), hospitalizations, regular follow-up visits and long-term rehabilitation periods. The consequences of non-compliance are considerable in terms of resource utilization and socio-economic well-being of patients.

Although overall compliance in this study was relatively good, the 47.6% of patients on concomitant therapy with PPIs may not have received maximum therapeutic effect from their treatment due to the antagonistic effect of combining PPIs and bisphosphonates. On this note, it is thus recommended that scheme protocols discourage concomitant use of PPIs and bisphosphonates. This will not only maintain the antifracture activity of the bisphosphonates, but also reduce the pill burden to the patient as well as limit treatment costs. In addition, many patients would benefit from taking Fosavance®, which will also reduce the pill burden and treatment costs.

Perhaps, it may be best that elderly patients and patients with a particular risk profile are allowed access to bisphosphonate formulations that are associated with minimal GIT adverse effects. The advantages of using Aclasta® far outweigh the use of cheaper options such as Osteobon® 70 mg in terms of the overall costs in osteoporosis management, convenience and compliance. As stated by Cramer (1995), : “current healthcare systems pay for high-technology treatments (such as expensive coronary bypass surgery and organ transplantation) but refuse to pay for inexpensive, preventive programs (such as risk reduction programs). Compliance enhancement requires some

time and some money, but it is a big bargain compared with management of an uncontrolled medical disorder or hospitalization".

In conclusion, further research is recommended to establish a more realistic status of osteoporosis management in this managed care organization, and the resulting burden it puts on the socio-economic status of those affected by osteoporosis and determine reasons why patients are not adhering to their treatment. This would then enable implementation of resolutions that would encourage and drive adherence and optimal treatment of osteoporosis.

Although low compliance was expected, in this study group compliance was relatively good. This indicates that the first hypothesis is false (hypothesis that the real life data affirm that compliance to bisphosphonates when used for the osteoporosis indication is low. This hypothesis is therefore rejected. There was a correlation between the age of patients and compliance, proving the second hypothesis to be true. Elderly patients had a higher compliance level than those below the age of 65 years. The results however do confirm the occurrence of bisphosphonate-induced gastrointestinal adverse effects, as reflected by the increased utilization of PPIs. This proves the third hypothesis to be true. In the absence of a predictor for the susceptibility to gastrointestinal adverse effects, it may be best to allow all patients to have access/an opportunity to use the most convenient dosing regimen.

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APPENDIX I – ATTACHMENTS

A. University of the Witwatersrand Human Research Ethics Committee Clearance Letter

B. Provident Healthcare Risk Managers Permission Letter to access their data

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Tirhani L Maluleke

CLEARANCE CERTIFICATE	**M10923**
PROJECT	Resource Utilization in the Management of Osteoporosis in South Africa: Analysis of Private Health Care
INVESTIGATORS	Ms Tirhani L Maluleke.
DEPARTMENT	Department of Pharmacy & Pharmacology
DATE CONSIDERED	01/10/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 01/10/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Neil Butkow

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

PROVIDENCE
Healthcare Risk Managers

20/08/2010

Dr Neil Butkow
Lecturer: Department of Pharmacy and Pharmacology University of the Witwatersrand
Medical School
7 York Rd
Parktown
2193
Johannesburg
South Africa

Dear Dr Butkow

APPROVAL FOR CLAIMS DATA

I hereby wish to inform you that PROVIDENCE Healthcare Risk Managers grants you/your Master's degree student the right to use the data provided to you for academic purposes.

We wish you every success with your/ your student's study and look forward to the outcome of your research.

Kind regards

J WEPENER
Manager: Pharmacy Benefit Management