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Breaking Point

The economic cost of not adhering to bisphosphonate treatment for osteoporosis

Report by Access Economics Pty Limited for

Roche Products Pty Limited and GlaxoSmithKline

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FOREWORD

Osteoporosis is a major problem facing women and men around the world including the Australian community. More than half of older Australian women and perhaps a third of older Australian men will suffer an osteoporotic fracture during their lifetime. However osteoporosis is seriously under-recognised and under-treated. In fact, less than two-thirds of women and probably even fewer men with low trauma, osteoporosis-related fractures currently receive specific therapy in Australia.

Even those who do start treatment may not continue as is the case in many other chronic health conditions. The analysis here considers some of the barriers to long-term adherence to treatment in those individuals in whom it is initiated. At the same time it tries to put an economic value on this failure to adhere to long term treatment.

Based on these analyses, improved compliance would be cost effective. Moreover simpler regimes that support better adherence may help to overcome some of the barriers to the initiation of treatment.

Thus this report identifies major costs and related health care issues that require careful evaluation and that must be fully addressed in concerted attempts to improve health care and community outcomes in osteoporosis.

Professor John Eisman

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GLOSSARY OF COMMON ABBREVIATIONS

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
BMD	bone mineral density
CPI	Consumer Price Index
DALY	disability adjusted life year
GP	general practitioner
NHS	National Health Survey
NPV	net present value
osteopenia	a deficit in BMD of between 1 and 2.5 standard deviations below the young adult reference mean
osteoporosis	a deficit in BMD of 2.5 standard deviations or more below the young adult reference mean
PBS	Pharmaceutical Benefits Scheme
QALY	quality adjusted life year
RAC	residential aged care
SDAC	Survey of Disability, Ageing and Carers (ABS)
VSL	value of a statistical life
YLD	years of healthy life lost due to disability
YLL	years of life lost due to premature mortality

EXECUTIVE SUMMARY

Osteoporosis is a significant cause of morbidity and mortality, largely due to fractures and their consequences. Osteoporotic fractures are associated with significant health system costs, informal care and other costs to the economy, including the loss of healthy life and wellbeing. Treatment of osteoporosis with bisphosphonates has been shown to be effective in reducing the risk of fracture by approximately 50%. However, there is growing concern that there is poor awareness of the diagnosis of osteoporosis and low rates of treatment even in those with documented osteoporosis or fracture. Furthermore, the risk reduction is not being achieved because of high levels of non-adherence in patients who are prescribed bisphosphonate therapy. This report estimates the cost of such non-adherence, in terms of medication wastage and the cost of osteoporotic fractures resulting from failure to achieve the therapeutic benefit that would be achieved with full adherence.

Non-adherence

The term "*non-adherence*" refers to a failure to either:

- take medication correctly in terms of dosing and regime ("*compliance"*); or
- continue to take medication for the recommended duration of time ("*persistence with therapy*").

Non-adherence is an issue in relation to the management of a number of chronic diseases. Non-adherence to bisphosphonates in osteoporosis can be due to:

- the long duration required to generate optimal benefit from therapy;
- the silent nature of bone loss so that, before experiencing a severe fracture, the perceived risk among patients is often not sufficient to motivate them to comply with treatment guidelines and the benefits of treatment are not immediately apparent or 'visible' as osteoporosis is an asymptomatic condition;
- difficulties expressed by patients in taking their treatment, including side effects, inconvenience, cost, access issues, multiple morbidities, confusion and difficulty in remembering; and
- a lack of patient understanding of the importance of persisting with therapy in order to receive the benefits, possibly due in part to communication or follow-up problems in the patient-doctor relationship.

Osteoporosis

Clinical diagnosis of osteoporosis may be confirmed by:

1 The presence or history of an osteoporotic fracture;
   - osteoporosis is usually discovered through occurrence of low trauma fractures, triggering an investigation by treating clinicians; or

2 The finding of low bone mass in the absence of fracture;
   - osteoporosis is defined as a deficit in bone mineral density (BMD) of 2.5 standard deviations or more below the young adult reference mean in postmenopausal Caucasian populations, while osteopenia is a deficit in BMD of between 1 and 2.5 standard deviations below the young adult reference mean.

In 2005, there were 585,800 Australians who self-reported osteoporosis, the majority being women (496,400 women and 89,400 men). Self-reports of osteoporosis are likely to substantially under-estimate actual cases, as many people may be unaware of the state of their BMD, or even of an initial fracture, and may not have received a diagnosis. Indeed, there may be as many as 2 million Australians with osteoporosis or osteopenia. However, the results in this report are not dependent on estimates of osteoporosis prevalence.

Use of bisphosphonates

In Australia there are currently three bisphosphonate generic compounds marketed:

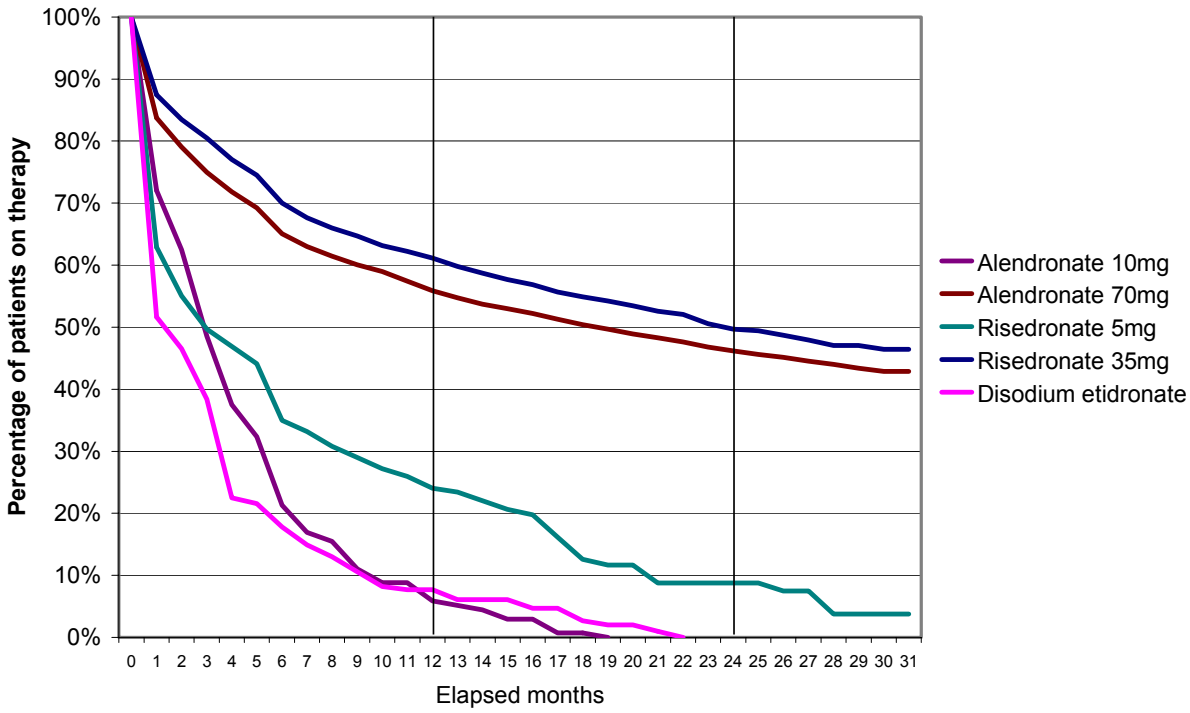
- alendronate (tradename: Fosamax, Alendro);
- disodium etidronate (tradename: Didrocal); and
- risedronate (tradename: Actonel).

There were an estimated 279,790 Australians who used bisphosphonates during 2005 that were subsidised by the Pharmaceutical Benefit Scheme (PBS). An estimated 98.9% of Australians currently receive weekly rather than daily therapy.

Persistence with therapy

Persistence with bisphosphonate therapy, by compound and strength, was greatest for weekly formulations (alendronate 70mg and risedronate 35 mg) with an estimated 56% and 61% respectively of patients still on therapy at 12 months. At 24 months, 46% of people remained on alendronate 70mg and 50% of people remained on risedronate 35mg.

PERSISTENCE WITH THERAPY – BISPHOSPHONATES



Adherence and the Medication Possession Ratio (MPR)

Persistence with therapy though is not an indication of adherence in terms of the medication used over time at the correct intervals. For example, if a patient has weekly therapy, then over a four week period the medication should be used at weekly intervals, after which the patient should obtain the next prescription. Since it is very difficult to determine the level of medication use among a patient group, a surrogate indicator has been used to indicate the actual level of use. **The Medication Possession Ratio (MPR), expressed as a percentage value, is the amount of therapy in possession by the patients at specific points in time.** For example a patient who only fills six prescriptions (four weeks of therapy for each prescription) over 12 months (52 weeks) has a MPR of 46% (24/52). The MPR is attempting to measure adherence on the interpretation that people who are filling their prescriptions are in fact taking the medication.

Previous sensitivity analysis has showed that a high level of adherence (MPR >80%) is required to obtain the fracture risk reduction in line with the published studies. The risk of bone fractures increases significantly among people with osteoporosis when the MPR is less than 80%. Conversely, an MPR of 80% or greater indicates good adherence with therapy and the likelihood of obtaining the therapeutic benefits.

Using the criterion of MPR greater than 80% as an indicator of adherence, other studies have estimated adherence with therapy to be 30.6% to 55.3% for weekly medications and 19.4% to 40.4% for daily medications.

The MPR indicator was used in conjunction with PBS data to estimate adherence with bisphosphonate therapy in Australia over 12 months worth of therapy (equivalent to 13 dispensed medications). The main limitation inherent in using PBS claims data is that it was not possible to determine the level of loss to follow-up because of mortality in the analysis, although from population-based mortality rates and even allowing for increased risk of mortality due to osteoporosis, mortality loss is considered to be low (under 5% over the year). The analysis compared people initiated on therapy as well as those already on bisphosphonates.

- For patients initiated on bisphosphonates at the beginning of 2005, 40.7% were in possession of 12 months of therapy (13 dispensed medications). After 12 months, 38.5% of bisphosphonate patients were in possession of <80% of therapy (1-9 medications dispensed) and considered not to be adhering with therapy.
- **For all people taking bisphosphonates during 2005**, only 27.9% were in possession of 12 months of therapy (13 dispensed medications) and **40.9% of bisphosphonate patients were in possession of <80% therapy (1-9 medications dispensed) and deemed not to be adhering with therapy.**

MEDICATION POSSESSION RATIO – ALL PATIENTS ON BISPHOSPHONATES, 2005

Medications	N	%	Cumulative %
13	78,060	27.9	27.9
12	46,720	16.7	44.6
11	24,060	8.6	53.2
10	16,510	5.9	59.1
9	13,150	4.7	63.8
8	10,910	3.9	67.7
7	10,070	3.6	71.3
6	12,870	4.6	75.9
5	10,910	3.9	79.8
4	10,630	3.8	83.6
3	11,750	4.2	87.8
2	14,280	5.1	92.9
1	19,870	7.3	100

Source: HI Connections analysis of data supplied by Medicare Australia. Totals may not sum due to rounding. Shaded cells represent people adhering on the basis of MPR≥80%.

Both groups of bisphosphonate patients showed around 60% in possession of >80% therapy (10-13 medications dispensed), although for a prevalence-based costing the estimate of 40.9% is the appropriate parameter to use. **Thus 40.9% of 279,790 bisphosphonate users or an estimated 114,434 people in 2005 are not adhering to therapy** and are most likely not receiving the full anti-fracture benefits. Furthermore, it is estimated that **these patients on average are recipients of 4.65 dispensed medications during the 12 month period**.

Fracture rates

The number of fractures due to non-adherence was based on the estimated number of Australians not adhering to their therapy in 2005 (114,434) multiplied by the expected fracture rates for males and females. There is some uncertainty surrounding the expected fracture rates. Lower bound estimates for the fracture rates were conservatively derived from the average of hospitalised fracture rates from AIHW data and previous expert group estimates as 1.3% for women and 0.7% for men. However, for Australians eligible for PBS-funded bisphosphonate therapy, the fracture rates are higher than the average population rate, since to be eligible a person must have experienced at least one fracture. In line with the body of evidence, the risk of any subsequent fracture once a first fracture has occurred is around fourfold, called the 'cascade effect'. The upper bound estimates were thus four times the lower bound estimates, with the base case estimates at the mid-points.

- In the base case, with fracture rates of 3.25% and 1.75% for females and males respectively, there were an estimated 3,133 female bisphosphonate patients with fractures resulting in hospitalisation and 316 male patients who experienced hospitalised fractures in 2005. However, bisphosphonates only reduce the risk of fracture by an estimated 50%. The unrealised effects of fracture reduction because of non-adherence are thus estimated to result in an excess of 1,724 total fractures because of non-adherence with bisphosphonates in 2005.
- In the high case sensitivity analysis (with fracture rates of 5.2% and 2.8%), there are an estimated 2,759 excess fractures due to non-adherence.
- In the low case sensitivity analysis (with fracture rates of 1.3% and 0.7%), there are an estimated 690 excess fractures due to non-adherence.

FRACTURES FOR BISPHOSPHONATE NON-ADHERENCE 2005

	Males	Females	Total
Bisphosphonate patients	44,110	235,680	279,790
Non-adhering patients	18,041	96,393	114,434
Fracture rate (base case)	1.75%	3.25%	-
Fractures predicted	316	3,133	3,448
Excess fractures	158	1,566	1,724
Fracture rate (high scenario)	2.8%	5.2%	-
Fractures predicted	505	5,012	5,517
Excess fractures (upper bound)	253	2,506	2,759
Fracture rate (low scenario)	0.7%	1.3%	-
Fractures predicted	126	1,253	1,379
Excess fractures (lower bound)	63	627	690

Note: Numbers may not sum due to rounding.

Costs of fractures from non-adherence

The costs associated with a fracture in an osteoporosis patient can include the following:

- greater health system utilisation, including acute hospitalisation, admission to residential aged care and rehabilitation;
  - consultation and dispensing costs are generated when a course of medication is commenced and, if non-adherence occurs, there is also the additional cost of medication wastage if a prescription is dispensed but not all the medication is used;
- loss of productivity in the paid and voluntary workforce (eg, capacity to care for a spouse or significant other);
- greater need for personal care and household services provided either by informal family carers or by formal sector community care services;
- greater need for aids, equipment or home modifications, largely to enhance mobility; and
- reduced quality of life, both as a result of the morbidity (pain and suffering from the fracture and associated disability), co-morbidity (eg, associated depression) and premature mortality (death) – known as the 'burden of disease'.

Findings

The level of non-adherence and subsequent fracture in Australia in 2005 is associated with estimated **financial costs of $83.3 million ($51.2 to $115.5 million) and the value of the healthy life lost of $102.8 million ($41.1 to $164.5 million) for a total economic burden of $186.1 million ($92.3 to $280.0 million).**

- Informal care accounts for the greatest cost ($30.1 million), followed by medication wastage ($29.8 million), residential aged care ($11.7 million), hospital expenditure ($8.5 million) and rehabilitation and other health system costs ($2.6 million).

ECONOMIC IMPACT OF NON-ADHERENCE WITH BISPHOSPHONATES, 2005

	Base case	High scenario	Low scenario
Health system cost ($m)	22.8	36.5	9.1
- *Hospital ($m)*	8.5	13.5	3.4
- *Residential aged care ($m)*	11.7	18.8	4.7
- *Rehabilitation/other ($m)*	2.6	4.1	1.0
Medication wastage ($m)	29.8	29.8	29.8
Productivity ($m)	0.6	0.9	0.2
Informal care ($m)	30.1	48.1	12.0
Mobility aids ($m)	0.1	0.2	0.0
Total financial costs ($m)	83.3	115.5	51.2
Lives lost	69	110	28
Life years lost (YLL)	324	518	129
Years life lost to disability (YLD)	309	494	124
QALYs	632	1012	253
Quality of life lost ($m)	102.8	164.5	41.1
Total financial and QOL cost ($m)	186.1	280.0	92.3

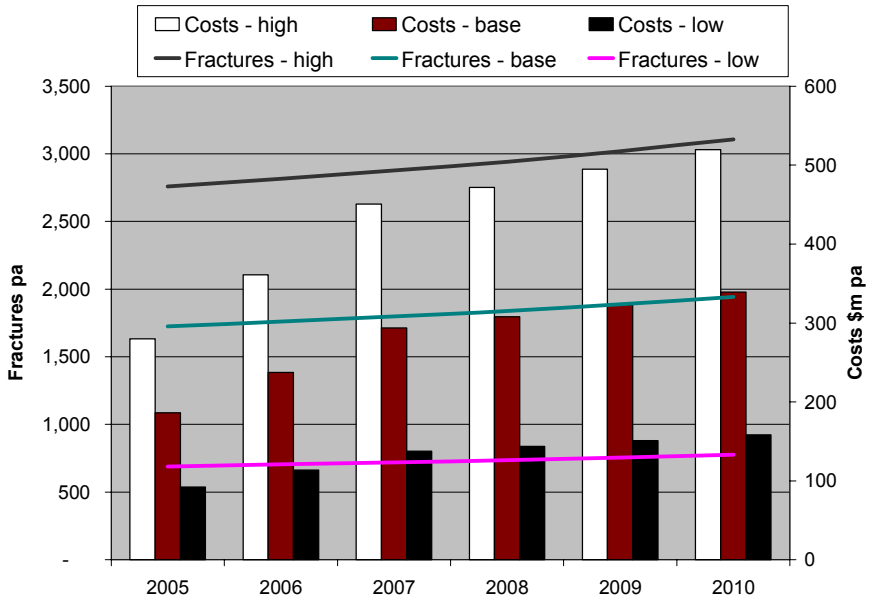
Cost projections

Costs of non-adherence were projected from 2005 to 2010 by projecting the number of people on bisphosphonates in line with growth in the population aged 65 years and over (separately for males and females). Non-adherence was projected to remain at 40.9% with the same fracture rates. Depending on the type of cost, costs projections were inflated by either projected health cost inflation, the Consumer Price Index or Average Weekly Earnings, from the Access Economics macroeconomic model forecasts.

- Some cost items were likely to be cumulative, including residential aged care, informal care, productivity losses and mobility aids, with the expected life of these costs estimated as three years on average.

Over 2005-2010, there are projected to be 10,950 fractures due to non-adherence in the base case, with a NPV of $1.7 billion ($0.8 billion to $2.6 billion) of which $1.0 billion ($0.5 billion to $1.5 billion) is the NPV of the financial costs and $647 million ($259 million to $1.0 billion) is the NPV of the value of the healthy life lost.

PROJECTED FRACTURES AND COSTS: BASE, HIGH AND LOW SCENARIOS, 2005-2010



Conclusions

Although there is still a large undetected level of osteoporosis in the population, over the past five years there has been an improvement in its detection. Currently available bisphosphonates are effective in the treatment of osteoporosis, with an increase in their use in Australia over the period. However, many of their benefits are not likely being realised because of low rates of treatment with bisphosphonates. In addition in those who are prescribed bisphosphonates there is an issue of non-adherence with therapy that is compounding this. It is misleading to think that because a patient has been identified with osteoporosis and has been prescribed a bisphosphonate that the therapeutic benefit has been realised. Osteoporosis is not unique in the issue of poor adherence to therapy. With increasing numbers of efficacious self-administered treatments, the need is apparent for better understanding and management of non-adherence in medications.

Simplified dosing regimens and reducing oral bisphosphonate frequency of administration are important factors for improving therapy convenience and practicality, with the hope of improving compliance and persistence. Evidence shows that once-monthly dosing plus patient support improves adherence relative to weekly dosing, while still below 60%. However, the levels of adherence and therefore therapeutic benefit are still sub-optimal, even with almost all patients now on weekly dosing in Australia.

Other factors may also contribute to achieving full adherence to realise the benefits of bisphosphonates for fracture risk reduction. The majority of non-adherents discontinue after the first prescription, and acceptance of therapy is crucial for long-term persistence. Measures to improve adherence might include improved physician/patient communication, close monitoring and early intervention in declining adherence, and strengthening of patient commitment through reinforcement of the connection between treatment response and quality of life benefits. Improved adherence with osteoporosis treatment also requires that treatment side effects be minimised, and that patients are informed of the biological markers that show bone strength and reduction in fragility. However, more research is necessary in this area.

Access Economics
October 2006

1. BACKGROUND

Access Economics was commissioned by Roche Products Pty Limited and GlaxoSmithKline to investigate the demographic prevalence, financial cost and disease burden from non-adherence in Australia to bisphosphonates, a therapeutic class of osteoporosis medication.

The term "*non-adherence*" refers to a failure to either:

- take medication correctly in terms of dosing and regime ("*compliance"*); or
- continue to take medication for the recommended duration of time ("*persistence with therapy*").

This report quantifies the health system and other economic impacts of non-adherence with bisphosphonates for the management of osteoporosis. People not adhering to medication do not receive the benefits of the medication (prevention of fractures) and costs are generated as a result of a consequent fracture. The costs associated with a fracture in an osteoporosis patient can include the following:

- greater health system utilisation, including acute hospitalisation, admission to residential aged care and rehabilitation;
  - consultation and dispensing costs are generated when a course of medication is commenced and, if non-adherence occurs, there is also the additional cost of medication wastage if a prescription is dispensed but not all the medication is used;
- loss of productivity in the paid and voluntary workforce (eg, capacity to care for a spouse or significant other);
- greater need for personal care and household services provided either by informal family carers or by formal sector community care services;
- greater need for aids, equipment or home modifications, largely to enhance mobility; and
- reduced quality of life, both as a result of the morbidity (pain and suffering from the fracture and associated disability), co-morbidity (eg, associated depression) and premature mortality (death) – known as the 'burden of disease'.

The study adopts a prevalence approach to cost measurement, measuring the number of people taking bisphosphonates, the level of non-adherence and the consequent fractures and costs for these people for the year 2005. There are essentially two ways of estimating each element of cost for each group:

- **Top-down:** The data may provide the total amount of a cost element eg, health system expenditure calculated by the Australian Institute of Health and Welfare (AIHW) for particular categories of the International Classification of Disease; or
- **Bottom-up:** The data may provide estimates of the number of cases in the category ('n') and the average unit cost for that category. The product is the total cost (eg, the wage rate for lost earnings multiplied by the average number of workdays lost and the number of people to whom this applies).

It is generally more desirable to use top-down national datasets in order to derive national cost estimates for large and well-studied diseases such as osteoporosis rather than extrapolate bottom-up data from smaller partial datasets. Bottom-up approaches thus tend to be used only when top-down data are not available. When this has been necessary in this study to

obtain parameters, there has been careful analysis of datasets and a literature review focusing on Australian literature but sometimes supplemented by international material.

The following chapters present evidence in relation to:

- the prevalence of osteoporosis, of fractures and of non-adherence with bisphosphonates (Chapter 2);
- the financial costs of non-adherence (Chapter 3); and
- the loss of healthy life or ‘burden of disease’ (Chapter 4).

2. OSTEOPOROSIS

2.1 EPIDEMIOLOGY

2.1.1 DEFINITION, DIAGNOSIS AND AETIOLOGY

The World Health Organization (WHO) defines osteoporosis as a "disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (WHO, 2003). Osteoporosis occurs when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

Clinical diagnosis may be confirmed by:

1 The presence or history of osteoporotic fractures;

- osteoporosis is usually discovered through occurrence of a low trauma fracture triggering an investigation by treating clinicians; or

2 The finding of low bone mass in the absence of fracture;

- osteoporosis is defined as a deficit in bone mineral density (BMD) of 2.5 standard deviations or more below the young adult reference mean in postmenopausal Caucasian populations (Kanis, 1994), while osteopenia is a deficit in BMD of between 1 and 2.5 standard deviations below the young adult reference mean (Sambrook et al, 2002).

Bone mineral density (BMD) is used as a measure of fracture risk with each standard deviation decrease in BMD being associated with an approximate twofold increase in the risk of fracture (Marshall et al, 1996).

The two major non-modifiable risk factors for osteoporosis are age and female gender. One in two women and one in three men over the age of 60 will have a fracture due to osteoporosis (Sanders et al, 1999a). Women are more likely to develop osteoporosis post menopause as the level of oestrogen, which is important for maintaining healthy bones in women, significantly decreases. The bones subsequently lose calcium and other minerals at a faster rate than that of pre-menopausal women.

2.1.2 FRACTURE RISK AND THE CASCADE EFFECT

The single most easily recognised risk factor for a future osteoporotic fracture is the presence of any vertebral or non-vertebral fragility fracture (Ross et al, 1991). Once one fracture has occurred, the chances of having another fracture are much higher compared to someone who has not had any fractures. This is called the 'cascade effect'. The literature varies in relation to the exact extent of the increased risk, which also depends on type of fracture, number of prior fractures, age and severity of osteoporosis.

- Women with pre-existing vertebral fractures have a risk of subsequent vertebral fractures about four times greater within the next year than those without prior fractures (Klotzbuecher et al, 2000).
- The risk of future fracture increases with the number of prior vertebral fractures. People who have had three or more fractures are 11 times more likely to have another fracture compared to someone who has not had a prior fracture (Klotzbuecher et al, 2000).

  - In the six months following a vertebral fracture, Johnell et al (2001) estimated that people aged 50-54 years have a 30 to 50-fold increased risk of suffering another.
- The risk of hip fracture increases after one or more vertebral fractures (Klotzbuecher et al, 2000).
- For any fracture, Marshall et al (1996) estimate the increase risk of a subsequent fracture as 1.5 to 2 fold.
- People who have suffered five or more fractures are 10 times more likely to experience another (Nevitt et al, 1999).
- The risk of forearm fracture is higher if there has been a previous forearm fracture. Of patients who have had a distal forearm fracture, 46% of women and 30% of men suffered further fractures over the following seven years (Cuddihy et al, 1999).
- Phillips and Braddon (2004) show fracture risk (any fracture) increasing from 0.25% for post-menopausal women over 60 with no osteoporosis or fracture, to 4.2% with osteoporosis and no fracture, and then to 12% for osteoporosis and at least one existing fracture, over a five year period.

In line with the whole body of evidence, the risk of any subsequent fracture once a first fracture has occurred is estimated in this report to be around fourfold.

Other common risk factors for osteoporotic fractures (Nguyen et al, 2004) include family history of fracture; inadequate dietary calcium intake; sedentary lifestyle or physical inactivity; smoking; excessive alcohol intake; early or surgically induced menopause; short duration of reproduction lifetime (ie, late menarche and/or early menopause); gonadotropin-releasing-hormone agonist therapy; anorexia nervosa; low testosterone levels in men; vitamin D deficiency; low body weight; hyperthyroidism; and the use of corticosteroids.

2.1.3 MORTALITY AND MORBIDITY FROM FRACTURES

Osteoporotic fractures, commonly of the hip, spine, humerus, forearm and wrist, are typically sustained with little or no antecedent trauma (Nguyen et al, 1993). However, morbidity from fractures includes pain, deformity, being bed-ridden; reductions in independence and activities of daily living (Nevitt et al, 1998); fear of falling; anxiety; social isolation and emotional disturbances such as depression (Salkeld et al, 2000). Fractures are associated with excess rates of nursing home admissions (Cumming et al, 1997) and reduced quality of life (Johnell et al, 2002; Martin et al, 2002). Hip fractures can be particularly disabling, with complications that, as with other fractures, can result in death (Center et al, 1999; Cauley et al, 2000).

All major osteoporotic fractures are associated with a twofold increase in age-adjusted mortality in women and a threefold increase in men (Randell et al, 2000). The relative risk of mortality is estimated to be 60% higher in women with vertebral fracture than in women without one (Ismail et al, 1998). The probability of death in the first year after a hip fracture is estimated at 10–20% (Cummings et al, 1998; Cooper et al, 1993; Cumming et al, 1997). Approximately half of the survivors are disabled and need help with activities of daily living, or even require long-term nursing care (Sernbo and Johnell, 1993; Beatriz and Perry, 1994).

2.1.4 PREVALENCE OF OSTEOPOROSIS IN AUSTRALIA

Osteoporosis has been considered under-diagnosed and under-treated in Australia since the early 1990s (Jones et al, 1994; Sanders et al, 1999b; Henry et al, 2000; Cooley and Jones, 2001; Nguyen et al, 2004). Most recently, Inderjeeth et al (2006) identified a significant lack of

awareness, diagnosis and treatment of patients with documented fracture up to six months following discharge from a tertiary hospital institution, ie, even in a high-risk osteoporotic fracture group.

Based on BMD it was estimated that as many as 11% of men and 27% of women aged 60 years or older have osteoporosis, and another 42% of men and 51% of women would be considered osteopenic (Nguyen and Eisman, 1999). The Geelong Osteoporosis Study estimated 35.6% and 50.1% prevalence of osteoporosis for people aged 70-79 years and over 80 years respectively. The 2001 National Health Survey (NHS) conducted by the Australian Bureau of Statistics (ABS) showed only 12.5% of women and 2.5% of men aged 65 years or older self-reported a diagnosis of osteoporosis (ABS, 2004). The ABS self-report data were based on whether the person had 'ever been told' by a doctor or nurse that they had osteoporosis (together with other sequenced indications) and the ABS notes that "presence of the condition is often not known or even suspected until medical diagnosis. Results from this survey therefore expect to significantly under estimate the true prevalence of the condition throughout the community" (ABS, 2006b). Access Economics (2005) estimated population prevalence of osteoporosis for 2005. These estimates were based on the levels reported in the 2001 National Health Survey. These estimates were then applied to the estimated population within Australia for 2005. The estimated number (for 2005) of males with osteoporosis was 57,700 and the estimated number of females with osteoporosis was 272,300.

During 2004-2005 the ABS NHS was conducted a third time utilising a similar sampling and questionnaire framework as for the 2001 and 1995 surveys (ABS, 2006a,b). The figures reported in the most recent survey (Table 2-1) are markedly higher than the previous ABS estimates. The 2004-05 NHS data showed that 89,400 males and 496,400 females self-reported a diagnosis of osteoporosis, a difference of 253,700 more people than the previous estimate for the period. The increase on the previous forecast is likely to be associated with substantial improvements in disease recognition and awareness, even over such a short period of time, although given the estimated levels of poor bone health (Nguyen and Eisman, 1999) and population fracture rates there is still a significantly under-diagnosed level of osteoporosis in Australia.

TABLE 2-1 SELF-REPORTED OSTEOPOROSIS IN THE GENERAL POPULATION, 2005

Age group (years)		0-34	35-44	45-54	55-64	65-74	75+	Total
Males	N	7,800	2,900	9,100	22,800	25,100	21,700	89,400
	%	0.2	0.2	0.7	2.1	3.8	4.7	0.9
Female	N	9,100	22,400	50,500	116,900	133,900	163,600	496,400
	%	0.2	1.5	3.6	11.1	19.3	26.2	5.0
Persons	N	17,000	25,300	59,600	139,700	159,000	185,300	585,800
	%	0.2	0.9	2.2	6.6	11.7	17.1	3.0

Source: ABS (2006a) and supplementary data request.

Clearly the self-reported data fall well short of the 11% and 27% osteoporosis prevalence in men and women over 60 years estimated by Nguyen and Eisman (1999). Indeed, it would appear that around 1 osteoporosis case in 2 for women and 2 in 3 for men is not self-reported. Including osteopenia also, the number of cases may be some ten times the NHS numbers for men and five times for women. Access Economics (2001) assessed the number of people who have sustained a fracture based on fracture rates and hospitalisations data and concluded there may be as many as 2 million cases of osteoporosis in Australia. The rate and

estimated number of fractures is addressed in Section 2.4. The results in this report are not dependent on estimated osteoporosis prevalence but on fracture prevalence.

2.2 BISPHOSPHONATES AND OSTEOPOROSIS

2.2.1 TREATMENT PATHWAY

Important principles of osteoporosis management are maximising bone mass and preventing (in women) post menopausal bone loss (O'Neill et al, 2004). Furthermore, the purpose of medication treatment in osteoporosis is to reduce morbidity and mortality associated with the first fracture and all subsequent fractures (Sambrook et al, 2002). The treatment of osteoporosis is warranted because:

- fractures are associated with significant morbidity and mortality;
- bone loss and fracture risk increase with advancing age; and
- treatments are available to prevent accelerated bone loss, slow the deterioration of the bone's microarchitecture and reduce the subsequent risk of fractures.

There is a broad range of pharmacotherapies for osteoporosis, from over-the-counter medications such as calcium and vitamin D, to oestrogen therapy, newer medications such as the Selective Estrogen Receptor Modulators (SERMs) and bisphosphonates.

Oral, nitrogen-containing bisphosphonates, given once-daily or once-weekly, are currently a common treatment for people with osteoporosis who have experienced a fracture. Bisphosphonates represent a class of medications that have been developed for patients with osteoporosis and aim to improve the BMD levels in patients. Change in BMD is the result of the bone remodelling process (or bone turnover), in which microscopic amounts of bone tissue are removed (bone resorption) and then replaced with new tissue (bone formation) (Miller et al, 1999). In middle to late adulthood, with an increased rate of bone turnover, the rate of bone resorption is greater than the rate of bone formation, resulting in net bone loss both in trabecular and cortical bone. The aim of bisphosphonates is to inhibit the excessive bone resorption. The therapeutic benefit of bisphosphonates is their capacity to increase BMD and reduce the rate of bone turnover (particularly bone resorption), thereby reducing bone loss.

In Australia there are currently three bisphosphonate generic compounds marketed:

- alendronate (tradename: Fosamax, Alendro);
- disodium etidronate (tradename: Didrocal); and
- risedronate (tradename: Actonel).

To optimise bioavailability and maximise upper gastrointestinal tolerability, patients taking oral bisphosphonates are required to adhere to stringent posture and pre- and post-dose fasting requirements. Examining the respective product information available in Australia (Table 2-2) describes the differing administration procedures:

TABLE 2-2 PRODUCT INFORMATION EXAMPLES, BISPHOSPHONATES

"Fosamax (Alendronate) must be taken at least 30 minutes before the first food, beverage or medication of the day with plain water only. Other beverages (including mineral water), food and some medications are likely to reduce the absorption of Fosamax (see Interactions). Fosamax should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, a Fosamax tablet should be swallowed with a full glass of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. Fosamax should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experience."
"The Disodium Etidronate (Didrocal) tablets should be taken as a single, oral dose at bedtime, preferably on an empty stomach. However, should gastrointestinal disturbance occur, the dose may be divided. To maximise absorption, patients should avoid taking the following within two hours of dosing: *- Foods, especially those high in calcium, such as milk or milk products.* *- Vitamins with mineral supplements or antacids which are high in metals such as calcium, iron, magnesium or aluminium."*
"Actonel (Risedronate) must only be taken with plain water. Actonel must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, Actonel should be taken in an upright position and the patient should avoid lying down for 30 minutes. Patients should not chew or suck on the tablet because of the potential for oropharyngeal irritation."

Source: Product Information – MIMS 2006.

Given the cost of bisphosphonates and the intended long term use, access to bisphosphonates for most people is through the Pharmaceutical Benefits Scheme (PBS). It is estimated that approximately 95% of bisphosphonate medications dispensed are paid for through the PBS with a relatively small private market. To receive subsidised bisphosphonate medications there are specific patient indications and eligibility criteria (Table 2-3).

TABLE 2-3 PBS INDICATIONS AND ELIGIBILITY CRITERIA FOR BISPHOSPHONATES

Use: *Initial treatment for established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be included in the authority application. Continuing treatment for established osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.* ***Note:*** *A vertebral fracture is defined as a >= 20% reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a >=20% reduction in any of these heights compared to the body above or below the affected one.*

Source: Pharmaceutical Benefits Scheme, 2006.[1]

[1] The indications and criteria are identical for: alendronate (Fosamax® - 70mg Weekly preparation now only available following withdrawal of Daily preparation from the Australian market); disodium etidronate (Didrocal® - Daily 200mg preparation available); and risedronate (Actonel® - Daily 5mg or Weekly 35mg preparation available).

The PBS indication requires a pre-existing fracture, which has precipitated debate. Most patients historically are diagnosed with osteoporosis as a result of a fracture. However as osteoporosis awareness and diagnosis from BMD measurements increase, there is likely to be an increased demand for medications by people with osteoporosis to prevent the first fracture and thus reduce overall fracture risk (because of the cascade effect). Currently people look for alternative treatments, including lifestyle modification (eg, exercise, nutrition) and the use of easier and more accessible medications (calcium and vitamin D supplements) to try and stave off first fractures. Hormone replacement therapy is also sometimes used to this end. While useful, the relative safety and efficacy of complementary therapies remains uncertain.

The Australian Fracture Prevention Summit recommended that bisphosphonate drug therapy be continued indefinitely for people with osteoporosis, because stopping treatment results in increased remodelling, bone loss, progression of structural damage and increased fracture risk (Sambrook et al, 2002). More recently, however, consensus is emerging among experts to recommend five years on treatment and then three to five years off, at least with the more potent nitrogen-containing bisphosphonates (Bone et al, 2004). Moreover, most of the increase in BMD from bisphosphonate use occurs within the first two years of treatment and the reduction in fracture rate is seen within 12–18 months (Cummings et al, 1998; Ettinger et al, 1999).

The effect of bisphosphonates on bone resorption suppression and increase in BMD significantly reduces the risk of vertebral fractures by 41-62% (Black et al, 1996; Harris et al, 1999; Reginster et al, 2000; Chesnut et al, 2004). Bisphosphonates have also been shown to produce significant risk reductions in non-vertebral fractures (20-69%) (Harris et al, 1999; Pols et al, 1999; McClung et al, 2001; Chesnut et al, 2004) and hip fractures (30-51%) (Black et al, 1996; Pols et al, 1999, McClung et al, 2001).

Alendronate and risedronate reduce the risk of single, multiple and morphometric (asymptomatic) vertebral fractures in women with osteoporosis and one or more baseline vertebral fractures by roughly 50% (Liberman et al, 1995; Black et al, 1996; Harris et al, 1999; Reginster et al, 2000). Alendronate also reduces the risk of vertebral fractures by about 50% in women who have osteoporosis without a pre-existing vertebral fracture Black et al, 1996; Harris et al, 1999).

Peripheral fracture rates are reduced with alendronate and risedronate in patients with a prevalent vertebral fracture. In alendronate sub-analysis there has been consistency in hip fracture risk reduction (Black et al, 1996). In one risedronate trial in which hip fractures were the primary endpoint, there was a 40% reduction in hip fracture risk among women aged 70–79 years with confirmed osteoporosis (McClung et al, 2001).

Although bisphosphonates prevent bone loss, lifelong treatment of women (or men) from the age of 50 years onwards can not be recommended except for those with osteoporosis (Sambrook et al, 2002), since they have not been shown to reduce fracture risk in women or men with normal BMD or in women or men with osteopenia with no history of fracture. Moreover, there is a lack of long term safety data on bisphosphonates beyond ten years.

2.2.2 BISPHOSPHONATE LEVELS OF USE

2.2.2.1 ABS SELF-REPORT DATA

Data from the 2005 NHS showed an estimated 585,800 persons who self-reported having osteoporosis – 89,400 males and 496,400 females. Of these, the same survey data estimated that 21,000 males (23.5% of males with osteoporosis) and 145,800 females (29.4% of females

with osteoporosis) have taken a bisphosphonate in the previous two weeks for osteoporosis, a total of **166,800** (Table 2-4). In line with prevalence of osteoporosis, there is a greater use of bisphosphonates among females and older age groups. These rates are similar to those in a study by Eisman in 2004 of over 9,000 GPs and 57,000 women aged 60 years and older that suggested that 20-30% of women with osteoporosis and/or fractures are treated. They are also consistent with Inderjeeth (2006:549), which showed bisphosphonate treatment in 20.7% of patients with previous fracture.

TABLE 2-4 BISPHOSPHONATE USE IN THE PREVIOUS TWO WEEKS, 2005

Age group (years)		0-59	60-69	70-79	80+	Total
Males	Osteoporosis	34,800	19,600	24,200	10,700	89,400
	Bisphosphonates	3,900	5,400	7,300	4,500	21,000
	% of osteoporosis	11.2	27.6	30.2	42.1	23.5
Female	Osteoporosis	147,200	114,300	139,000	96,000	496,400
	Bisphosphonates	22,700	38,000	51,100	34,000	145,800
	% of osteoporosis	15.4	33.2	36.8	35.4	29.4
Persons	Osteoporosis	182,000	133,900	163,100	106,700	585,800
	Bisphosphonates	26,600	43,400	58,400	38,400	166,800
	% of osteoporosis	14.6	32.4	35.8	36.0	28.5

Source: ABS NHS 2004-05 special data request. Numbers may not sum due to rounding.

2.2.2.2 PBS DATA

The majority of bisphosphonate use in Australia is subsidised under the PBS. Given that use of bisphosphonates under the PBS is only for people who have sustained a first fracture, the PBS data are a valuable source for the determination of patterns of bisphosphonate use amongst people with osteoporosis and fracture history in the Australian population. HI Connections[2] provided the PBS analysis used in this report. This analysis was based on data provided by Medicare Australia that was derived from PBS claims for bisphosphonates (alendronate, disodium etidronate and risedronate) for a 10% sample of the population.

General practitioners (GPs) prescribed most (95.3%) of the bisphosphonates dispensed in 2005 (Table 2-5), with females receiving 2,235,970 dispensed prescriptions and males receiving 368,490 dispensed prescriptions. The greatest number of bisphosphonate medications were for people aged 70-79 years (953,660) followed by those aged 80 years or more (783,850). The weekly formulation accounted for 98.9% of all bisphosphonates.

[2] HI Connections is a private consulting group specialising in the analysis of drug utilisation data

TABLE 2-5 BISPHOSPHONATES, DISPENSED PBS PRESCRIPTIONS, 2005

Age group (years)		0-59	60-69	70-79	80+	Total
GP	Males	51,680	81,860	133,870	74,020	341,430
	Females	206,520	471,880	777,730	685,460	2,141,590
	Total	258,200	553,740	911,600	759,480	2,483,020
Specialists	Males	8,770	5,060	10,360	2,870	27,060
	Females	17,690	23,490	31,700	21,500	94,380
	Total	26,460	28,550	42,060	24,370	121,440
Total	Males	60,450	86,920	144,230	76,890	368,490
	Females	224,210	495,370	809,430	706,960	2,235,970
	Total	284,660	582,290	953,660	783,850	2,604,460

Source: HI Connections analysis of data supplied by Medicare Australia.

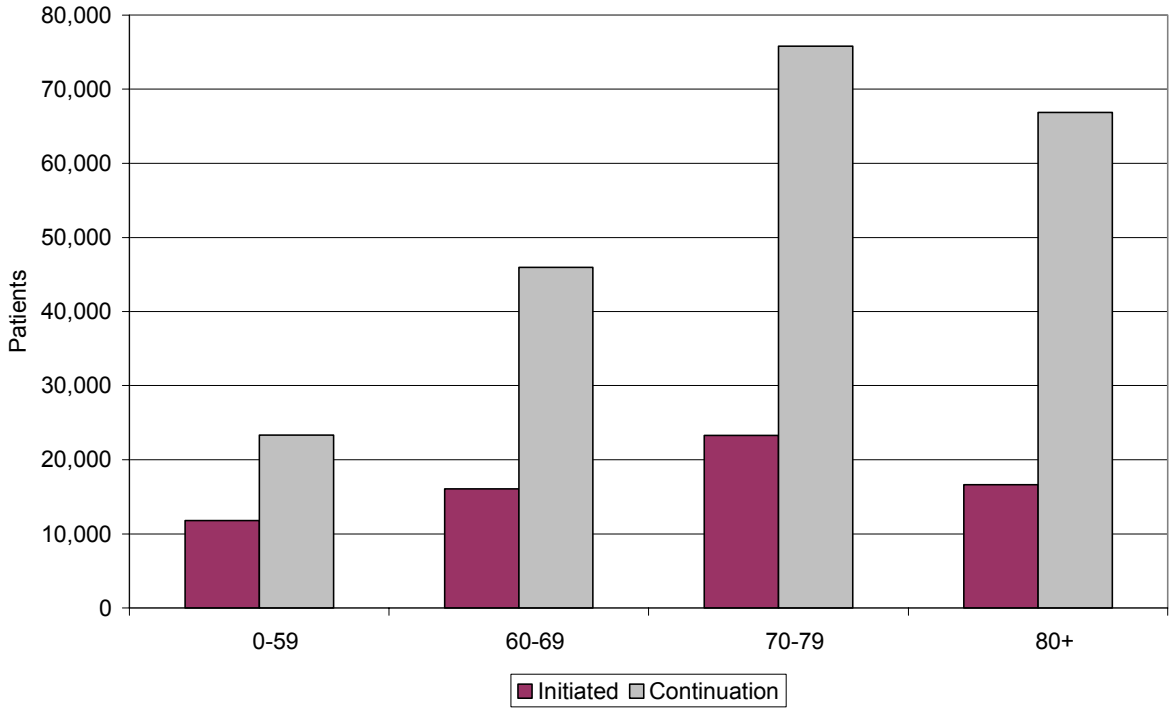
In calendar year 2005, there were 67,860 people who were initiated on bisphosphonates, while there were 211,930 people who were considered to have been continuing bisphosphonate therapy, for a total of 279,790 Australians taking bisphosphonates in 2005 (Table 2-6).

TABLE 2-6 BISPHOSPHONATE PATIENTS, PBS, 2005

Age group (years)		0-59	60-69	70-79	80+	Total
Initiated	Males	2,620	3,360	5,800	3,010	14,790
	Females	9,210	12,730	17,490	13,640	53,070
	Total	11,830	16,090	23,290	16,650	67,860
Continued	Males	5,100	6,660	11,150	6,410	29,320
	Females	18,230	39,300	64,630	60,450	182,610
	Total	23,330	45,960	75,780	66,860	211,930
Total	Males	7,720	10,020	16,950	9,420	44,110
	Females	27,440	52,030	82,120	74,090	235,680
	Total	35,160	62,050	99,070	83,510	279,790

Source: HI Connections analysis of data supplied by Medicare Australia.

FIGURE 2-1 PATIENTS INITIATED AND CONTINUED WITH BISPHOSPHONATES, 2005



Source: HI Connections analysis of data supplied by Medicare Australia

2.2.2.3 COMPARING THE ABS AND PBS DATA

The ABS NHS 2004-05 results, while estimating the prevalence of osteoporosis in the population, only provided a limited insight into the use of bisphosphonates, by focusing only on its use in the previous two weeks. It is possible to examine the use of bisphosphonates among people with self-reported osteoporosis over a full year by combining the ABS NHS 2005 osteoporosis prevalence data with the PBS medication use data (Table 2-7).

TABLE 2-7 PREVALENCE OF BISPHOSPHONATE USE IN PEOPLE WITH OSTEOPOROSIS, 2005

Age group (years)		0-59	60-69	70-79	80+	Total
Males	Osteoporosis[1]	34,800	19,600	24,200	10,700	89,400
	Bisphosphonates[2]	7,720	10,020	16,950	9,420	44,110
	% of osteoporosis[3]	22.2	51.1	70.0	88.0	49.3
	Not using	27,080	9,580	7,250	1,280	45,290
Female	Osteoporosis[1]	147,200	114,300	139,000	96,000	496,400
	Bisphosphonates[2]	27,440	52,030	82,120	74,090	235,680
	% of osteoporosis[3]	18.6	45.5	59.1	77.2	47.5
	Not using	119,760	62,270	56,880	21,910	260,720
Persons	Osteoporosis[1]	182,000	133,900	163,100	106,700	585,800
	Bisphosphonates[2]	35,160	62,050	99,070	83,510	279,790
	% of osteoporosis[3]	19.3	46.3	60.7	78.3	47.8
	Not using	146,840	71,850	64,030	23,190	306,010

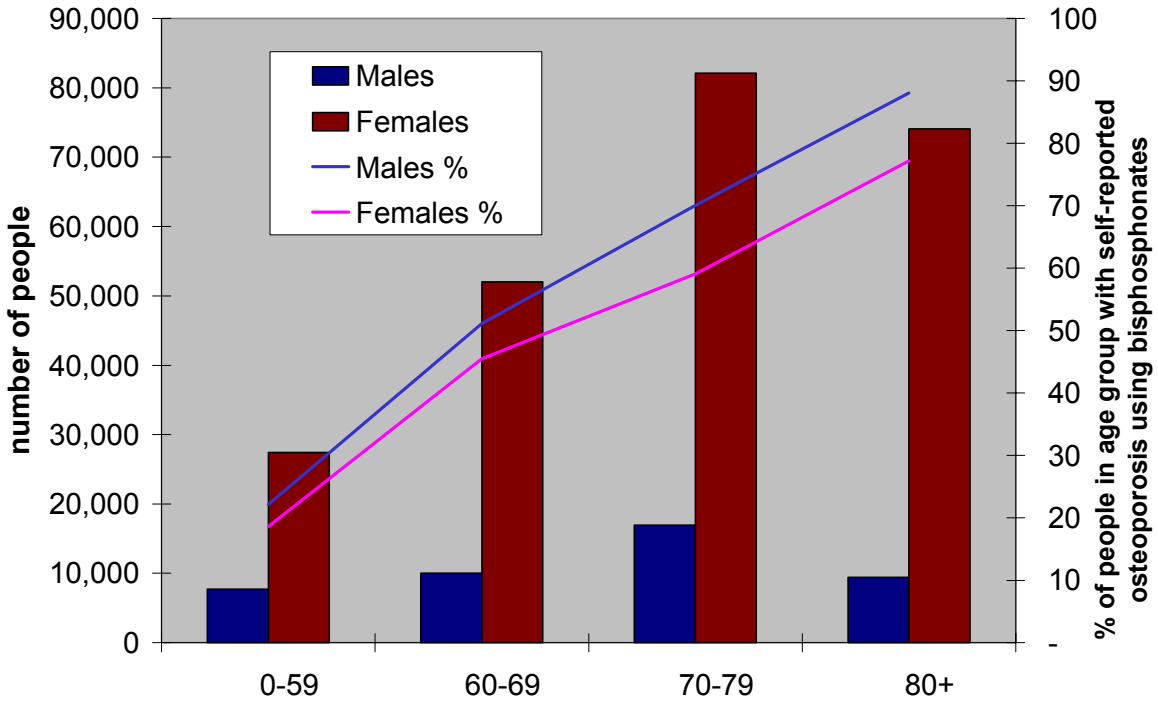
[1] Osteoporosis self-reported prevalence estimated from NHS 2004-05 data.
[2] Bisphosphonate use estimated from PBS 2005.
[3] Percentage of people with osteoporosis who have taken bisphosphonates during the 12 month period.
Note: Numbers may not sum due to rounding.

It is estimated that, overall, 47.8% of people with self-reported osteoporosis are using bisphosphonates with 306,010 patients with osteoporosis not using bisphosphonates. Older people are more likely to use bisphosphonates than younger people (Figure 2-2). For the age group at most risk of fractures (60 years or older) it is estimated that 159,070 people (39%) with self-reported osteoporosis are not using bisphosphonates[3]. Moreover, those people who have filled their PBS scripts for bisphosphonates may not be complying in terms of use and may not persist with therapy for a period sufficient time to achieve a therapeutic benefit.

It should be emphasised that the rates of usage of bisphosphonates by people with self-reported osteoporosis (using the combined ABS/PBS data) will necessarily be higher than the rates identified in the epidemiological studies or in the ABS NHS of around 20-30%. This is because of the under-estimation of osteoporosis in self-report data. However, once again this ratio is not utilised in the costing, but is included for triangulation purposes.

The findings concur with those of Eisman et al (2004), which also point to high proportions of Australian postmenopausal women having low trauma fracture after menopause but relatively low numbers on any regular therapy. Importantly, these also concluded from these Bone Care Study data that the focus on those aged 70-79 years or older may be five to ten years too late for the peak fracture risk.

FIGURE 2-2 BISPHOSPHONATE USE IN PEOPLE WITH SELF-REPORTED OSTEOPOROSIS, 2005



Note for the lines in the chart: The denominator is self-reported osteoporosis prevalence estimated from NHS 2004-05 data. The numerator is the prevalence of bisphosphonate use estimated from PBS 2005 data. The lines represent the derived percentage of people with osteoporosis who have taken bisphosphonates during the year.

[3] These people may, however, have previously used bisphosphonates, may use bisphosphonates in the future or may currently be using other medications or treatment options.

2.3 LEVEL OF NON-ADHERENCE WITH BISPHOSPHONATE MEDICATIONS

"*Non-adherence*" was defined in Chapter 1 as a failure to comply or persist with therapy. Adherence can be defined as the extent to which patients follow the instructions they are given for prescribed treatments (Haynes et al, 2005), in terms of dosing, regime and duration. The term "adherence" is intended to be non-judgmental – a statement of fact – and reflects a mutual or interactive responsibility shared by the physician and patient. To the extent that medication response is related to the dose and schedule of a medication, non-adherence reduces medication benefits. Low adherence with medication has been associated with poor outcomes (eg, mortality), even when the medication was a placebo (Irvine et al,1999).

Adherence with treatment among patients with chronic diseases is currently sub-optimal (Reginster et al, 2006b). Poor adherence leads to reduced therapeutic benefit, a raised incidence of secondary complications and therefore increased healthcare costs.

Many reasons exist for non-adherence with medication regimens, including (but not restricted to) problems with the regimen (such as adverse effects), poor instructions, poor provider-patient relationship, poor memory, patients' disagreement with the need for treatment or inability to pay for it (Solomon et al, 2005, 2004). Furthermore, adherence with medication is less likely when the treatment benefits are poorly understood by the patients (Haynes et al, 2005).

The International Osteoporosis Foundation (2006), based to some degree on findings from Sambrook (2006), suggested that non-adherence results at least in part due to:

- the long duration required to generate optimal benefit from therapy;
- the silent nature of bone loss so that, before experiencing a severe fracture, the perceived risk among patients is often not sufficient to motivate them to comply with treatment guidelines and the benefits of treatment are not immediately apparent or 'visible' as osteoporosis is an asymptomatic condition;
- difficulties expressed by patients in taking their treatment, including side effects, inconvenience, cost, access issues, multiple morbidities, confusion and difficulty in remembering; and
- a lack of patient understanding of the importance of persisting with therapy in order to receive the benefits, possibly due in part to communication or follow-up problems in the patient-doctor relationship.

Poor osteoporosis diagnosis and awareness amongst patients and clinicians may be another potential reason for non-adherence in those who have commenced treatment (Inderjeeth et al, 2006).

In clinical trials of medications adherence amongst patients may be good, but in practice with the wider population lower adherence with prescribed medication is very common. A review of 75 studies (Claxton et al, 2001) showed overall adherence for taking doses of 85 different regimens was 71%, with a range of 34% to 97% in individual studies. In a different review, typical adherence rates for prescribed medications were about 50%, with a range from 0% to over 100% (Haynes et al, 2005).

Suboptimal adherence is a major limitation to the long-term goals of osteoporosis treatment (Reginster, 2006). Specific attention by the patient is required to take bisphosphonates correctly. The stringent administration requirements may cause inconvenience for some

patients and lead to decreased long-term adherence with treatment, which may reduce anti-fracture efficacy (Miller, 2005).

The adverse event profile of bisphosphonates is also likely to affect medication adherence with therapy amongst patients. In particular, abdominal pains, diarrhoea, oesophagitis, oesophageal ulceration or oesophageal stricture have been commonly reported via spontaneous adverse drug reaction reporting mechanisms (ADRAC, 1999; de Groen et al, 1996) and via prescription event monitoring studies (Mackay et al, 1998). However, there is conflicting evidence from reviews of the clinical trial results, suggesting the incidence of upper adverse gastrointestinal events associated with bisphosphonate use are not significantly greater than placebo (Kherani et al, 2002; Bauer et al, 2000).

For patients with osteoporosis, long-term adherence with therapy is further complicated by the asymptomatic nature of the disease and the lack of options for patient self-monitoring (Reginster et al, 2006a). The non-adherence problem is cumulative – complex dosing guidelines contribute to poor compliance with therapy, and the failure to follow administration guidelines may increase the likelihood of treatment-related adverse events such as gastrointestinal disturbances, and intolerability that further reduce compliance and persistence with treatment (Tosteson et al, 2003; Cramer and Silverman, 2006).

Finally, given that the population most at risk and requiring treatment is elderly, this group has a significant number of comorbidities and requires polypharmacy for the management of their multiple medical problems. General practitioners and patients are advised to minimise polypharmacy because of the potential risk of drug interactions, side effects and an increased risk of falls i.e. with four or more medications (polypharmacy). This may be an additional reason why treatment for osteoporosis may be discontinued given the asymptomatic nature of the disease.

2.3.1 PERSISTENCE WITH THERAPY

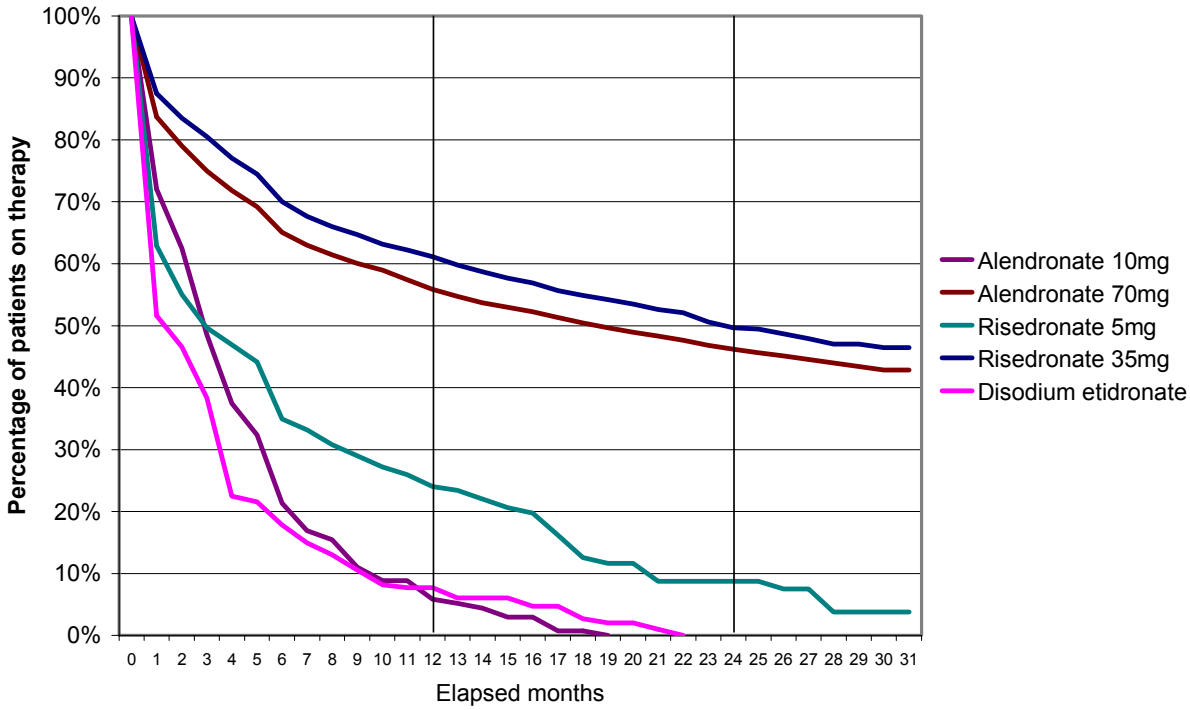
It has been estimated previously that 50% of patients discontinue daily bisphosphonate therapy within one year, negatively impacting on treatment outcomes and leading to a reduced anti-fracture effect (Reginster et al, 2006b). A study of UK medical records (Van Staa et al, 2005) revealed that after one year, 63.6% of patients taking bisphosphonate were persisting with treatment, falling to 45.5% after three years, with discontinuation most likely to occur during the early stages of treatment.

There are documented differences in persistence with therapy when one compares daily bisphosphonate with the weekly form. In a study by Recker et al (2005), only about one third of patients in the daily dosing group and fewer than one half in the weekly dosing group achieved persistence with therapy over a 12-month period. In a separate study by Cramer et al (2005), persistence with therapy for initiated weekly bisphosphonate medication was 44.2% at 12 months, while persistence with therapy for daily bisphosphonates was 31.7%. A similar study (Bartl et al, 2005) showed that weekly bisphosphonate use resulted in greater number of patients persisting with therapy at 12 months (46.5%) than daily bisphosphonate use (27.8%).

In analysis of PBS data by HI Connections Pty Ltd (May 2005) and presented by Sambrook (2006), 57% of patients starting medication for osteoporosis persisted with treatment after 12 months. It was further highlighted that, of the patients who discontinued therapy, the majority ceased taking treatment within the first six months. In examining bisphosphonates,

weekly preparations had a higher level of persistence at 12 months (60-70%) than daily preparations (20-30%).[4]

FIGURE 2-3 PERSISTENCE WITH THERAPY – BISPHOSPHONATES



Source: HI Connections analysis of data supplied by Medicare Australia.

Using more recent data from the PBS and provided by HI Connections, persistence with therapy was investigated for people initiated on bisphosphonates by compound and strength (Figure 2-3). Persistence with therapy was greatest for weekly formulations (alendronate 70mg and risedronate 35 mg) with an estimated 56% and 61% respectively of patients still on therapy at 12 months. At 24 months, 46% of people remained on alendronate 70mg and 50% of people remained on risedronate 35mg.

Previously (Section 2.2.2.2) it was mentioned that 98.9% of PBS bisphosphonate prescriptions dispensed during 2005 are the weekly formulation. A separate analysis of the persistence with therapy data for all bisphosphonates (Table 2-8) estimated that 56.9% of patients are persisting with therapy at 12 months, while 43.1% of patients have stopped using bisphosphonates by the end of the first year. In support of overseas data showing significant early drop, 15.4% of patients initiated to bisphosphonates did not continue beyond the first month of therapy.

[4] It is possible that some people initially on daily therapies may have changed over to weekly ones.

TABLE 2-8 PERSISTENCE WITH THERAPY - BISPHOSPHONATES

Months	n	% persistent	% non-persistent
0	178,810	100.0	0.0
1	151,350	84.6	15.4
2	143,250	80.1	19.9
3	136,433	76.3	23.7
4	130,534	73.0	27.0
5	125,863	70.4	29.6
6	118,038	66.0	34.0
7	114,174	63.9	36.1
8	111,303	62.2	37.8
9	108,856	60.9	39.1
10	106,585	59.6	40.4
11	104,175	58.3	41.7
12	101,689	56.9	43.1

2.3.2 MEDICATION IN POSSESSION

Persistence with therapy though is not an indication of adherence in terms of the medication used over time at the correct intervals. For example, if a patient has weekly therapy, then over a four week period the medication should be used at weekly intervals, after which the patient should obtain the next prescription. Since it is very difficult to determine the level of medication use among a patient group, a surrogate indicator has been used to indicate the actual level of use. The Medication Possession Ratio (MPR), expressed as a percentage value, is the amount of therapy in possession of the patient at specific points in time. For example a patient who only fills six prescriptions (four weeks of therapy for each prescription) over 12 months (52 weeks) has a MPR of 46% (24/52). The MPR is attempting to measure adherence on the assumption that people who are filling their prescriptions are in fact taking the medication.

A sensitivity analysis by Caro et al (2004) showed that a high level of adherence (MPR >80%) is required to obtain the fracture risk reduction in line with the published studies. In contrast the risk of bone fractures increases significantly among people with osteoporosis when the MPR is less than 80% than those osteoporosis patients with MPR greater than 80%. This means that if a patient has 80% of medication in their possession over a period of time then they are likely to have a good indicator of adherence with therapy and are therefore likely to be obtaining the therapeutic benefits.

In studies by Cramer et al (2005) and Bartl et al (2005) the MPR was significantly higher in patients receiving once-weekly bisphosphonates (65% and 69.2%) than in those receiving daily treatment (54% and 57.6%) over 12 months of follow-up. Using the criterion of MPR greater than 80% as an indicator of adherence, adherence with therapy was estimated in these two studies to be 30.6% to 55.3% for weekly medications and 19.4% to 40.4% for daily medications.

Despite the limitations inherent in using claims studies, the MPR indicator of high adherence with treatment, defined as drug available to cover 80% of the time, is associated with a significant reduction in fracture risk (Caro et al, 2004).

Using PBS data, an analysis of bisphosphonate MPR was undertaken (Table 2-9). The analysis followed patients over 12 months from their initiation date to determine the level of

filling of 12 months worth of therapy (equivalent to 13 dispensed medications). It was not possible to determine the level of loss to follow-up because of mortality in the analysis although this is considered to be low. It is shown that 40.7% of patients were dispensed 13 medications in the first 12 months.

- 61.5% of bisphosphonate patients were in possession of >80% therapy (10-13 medications dispensed) and deemed as having a high adherence with therapy.
- 38.5% of bisphosphonate patients were in possession of <80% of therapy (1-9 medications dispensed) and considered not to be adhering with therapy.

TABLE 2-9 MEDICATION POSSESSION RATIO – PEOPLE INITIATED ON BISPHOSPHONATES, 2005

Medications	N	%	Cumulative %
13	27,620	40.7	40.7
12	7,880	11.6	52.3
11	3,730	5.5	57.8
10	2,510	3.7	61.5
9	2,110	3.1	64.6
8	1,910	2.8	67.4
7	1,770	2.6	70.0
6	3,060	4.5	74.5
5	1,910	2.8	77.3
4	2,100	3.1	80.4
3	2,320	3.4	83.8
2	3,670	5.4	89.2
1	7,270	10.7	100.0

Source: HI Connections analysis of data supplied by Medicare Australia. Totals may not sum due to rounding.

The 12-month MPR was also recorded for all people taking bisphosphonates during 2005 (Table 2-10), showing that only 27.9% of patients were in possession of 12 months of therapy (13 dispensed medications).

TABLE 2-10 MEDICATION POSSESSION RATIO – ALL PATIENTS ON BISPHOSPHONATES, 2005

Medications	N	%	Cumulative %
13	78,060	27.9	27.9
12	46,720	16.7	44.6
11	24,060	8.6	53.2
10	16,510	5.9	59.1
9	13,150	4.7	63.8
8	10,910	3.9	67.7
7	10,070	3.6	71.3
6	12,870	4.6	75.9
5	10,910	3.9	79.8
4	10,630	3.8	83.6
3	11,750	4.2	87.8
2	14,280	5.1	92.9
1	19,870	7.3	100

Source: HI Connections analysis of data supplied by Medicare Australia. Totals may not sum due to rounding.

If we again use the same criteria of Caro et al (2004) for all patients dispensed with PBS subsidised bisphosphonates (Table 2-10):

- 59.1% of bisphosphonate patients are in possession of >80% therapy (10-13 medications dispensed) and have high adherence with therapy; while
- 40.9% of bisphosphonate patients are in possession of <80% therapy (1-9 medications dispensed) and deemed not to be adhering with therapy.

In contrast to patients initiated on bisphosphonates, the degree of adherence is slightly less when one considers all patients using therapy during 2005, regardless of when they began using bisphosphonates. That said, the numbers are not dissimilar to the ones for the people initiated on bisphosphonates. Both groups of bisphosphonate patients showed around 60% in possession of >80% therapy (10-13 medications dispensed).

These findings would estimate that 40.9% (114,434 people) of bisphosphonate users in 2005 are not adhering to therapy and are most likely not receiving the anti-fracture benefits of bisphosphonates.[5] Furthermore, it is estimated that these patients on average are recipients of 4.65 dispensed medications during the 12 month period.

2.4 NUMBER OF FRACTURES FROM NON-ADHERENCE

Osteoporotic fractures are characterised by low impact trauma events and tend to be referred to as “fragility” fracture. Among those aged over 60 years, osteoporotic fractures are relatively common and can be causes of long term disability. In Australia there have been three large prospective cohort studies investigating fracture epidemiology.

- The Dubbo Osteoporosis Epidemiology Study (DOES) of a cohort of about 1,600 men and 2,100 women with pre-fracture assessments reported 306 fractures in 3.25 years (1989–1992), giving an estimated residual lifetime fracture risk of 29% for men and 56% for women aged over 60 years (Nguyen et al, 1993).
- The Geelong Osteoporosis Study (GOS) of about 109,900 men and women aged over 35 years reported 2,184 fractures over two years (1994–1996), with an estimated lifetime risk of fracture of 42% in women aged over 50 years (Sanders et al, 1999b).
- The Tasmanian Older Adult Cohort (TASOAC) study of about 229,600 men and women of all ages reported 2,140 fractures over two years (1997–1999), with an estimated residual lifetime fracture risk of 27% for men and 44% for women aged over 50 years (Cooley and Jones, 2001).

From these studies, the total number of fractures each year among Australians aged over 60 years has been estimated at 73,000 (DOES), 57,000 (TASOAC) and 51,000 (GOS). Using a different methodology based on hospitalisations data, Access Economics (2001) previously estimated there were 65,000 osteoporotic fractures in Australia in 2001.

The current study requires estimation of the likely one-year prevalence of fractures in the non-adherent population for females and males. The estimate is derived from data from two sources – one providing a lower bound and the other an upper bound for the female

[5] It is possible that these people are perhaps getting some benefit as the effects of bisphosphonates on bone turnover can be prolonged. The effect of a single dose may last longer than the one week between dosing. Whilst there have been dose response studies there have not necessarily been comparative dose frequency studies on fracture outcomes, with the currently available bisphosphonates. There are however studies that show, for instance, alendronate has a prolonged effect in maintaining BMD once the active medication has ceased.

population. To be very conservative, and because only hospitalised fractures data are robust, the hospitalised fracture rate is used for both the lower and upper bound. An average is then calculated.

- The Australian Institute of Health and Welfare (AIHW, 2005a) conservatively estimated that the total cost of hospital inpatient care due to osteoporosis was $38.9 million at an average cost of $4,327 per separation in 2000-01. This suggests that around 9,100 people were discharged after an osteoporotic fracture in that year, a large proportion being females aged over 60 years. This represents a hospitalised fracture rate of 0.7%.
- In 2001, Access Economics provided a detailed estimation of the hospitalised fracture rate, based on data from the AIHW hospital morbidity database and the Geelong osteoporosis study, together with expert opinion, the proportion of ICD-9 conditions (the most recent at the time) that could be expected to include osteoporotic conditions and the attributable fractions thereof. From this, the estimated fracture rate was derived as 1.9% among women.

The average of these two estimates provides a one-year prevalence of hospitalised osteoporotic fractures to be 1.3% (0.7%-1.9%) of the female population. The one year prevalence rate of hospitalised osteoporotic fractures in Australian males is estimated to be 0.7% given the findings in the DOES and TASOAC whereby the lifetime risk is of hospitalised fractures in Australian males is approximately 40-50% lower than that of Australian females.

To determine the number of hospitalised fractures amongst people with osteoporosis the 'fracture rate' of 1.3% could be applied to the general female population and a 'fracture rate of 0.7% is applied for the general male population. However, the rate amongst the population of patients who are not in adherence with bisphosphonates is expected to be higher than these general fracture rates (which include people being treated who have lower fracture rates).

People with a history of prior fracture are at significantly increased risk of subsequent fracture. Section 2.1.2 concluded that the increased fracture rate for a subsequent fracture was around fourfold. Given that patients receiving PBS-subsidised bisphosphonates have already had a fracture to be eligible for subsidised therapy, these patients would have a higher fracture rate than the general population, although of course if they are adhering to their bisphosphonate therapy that risk is reduced by half. Another complexity is that, while it seems quite logical that higher fracture rates in non-adherent persons are due to the absence of therapy, a few (older) studies found that non-adherence to placebo was also associated with higher morbidity and mortality (Horwitz et al, 1990; Anon, 1980). Using a four-fold increase in the probability of a fracture for patients who have a prior fracture equates to a hospitalised fracture rate of 5.2% amongst female patients not adhering to therapy and a fracture rate of 2.8% amongst male patients not adhering to therapy. These rates represent an upper likely bound, while the 1.3% and 0.7% rates represent a likely lower bound. **Because of the uncertainty surrounding the actual fracture rates in the non-adherent population, a 'base case' is modelled at the mid-points of 3.25% and 1.75% for females and males respectively, with sensitivity analysis at the likely lower and upper bounds.**

Table 2-11 represents the results after applying the level of non-adherence for bisphosphonates (40.9%) to the number of bisphosphonate patients and then applying the sex-specific fracture rates under the base case and scenarios for 2005.

- In the base case (fracture rates of 3.25% and 1.75% for females and males respectively), an estimated 3,133 female patients with fractures resulting in hospitalisation and 316 male patients who experienced hospitalised fractures. However, bisphosphonates only reduce the risk of fracture by an estimated 50%. The unrealised effects of fracture reduction because of non-adherence actually result in an excess of 1,724 total fractures because of non-adherence with bisphosphonates in 2005.
- In the high case sensitivity analysis (5.2% and 2.8%), there are an estimated 2,759 excess fractures due to non-adherence.
- In the low case sensitivity analysis (1.3% and 0.7%), there are an estimated 690 excess fractures due to non-adherence.

TABLE 2-11 FRACTURES FOR BISPHOSPHONATE NON-ADHERENCE 2005

	Males	Females	Total
Bisphosphonate patients	44,110	235,680	279,790
Non-adhering patients	18,041	96,393	114,434
Fracture rate (base case)	1.75%	3.25%	-
Fractures predicted	316	3,133	3,448
Excess fractures	158	1,566	1,724
Fracture rate (high scenario)	2.8%	5.2%	-
Fractures predicted	505	5,012	5,517
Excess fractures (upper bound)	253	2,506	2,759
Fracture rate (low scenario)	0.7%	1.3%	-
Fractures predicted	126	1,253	1,379
Excess fractures (lower bound)	63	627	690

Note: Numbers may not sum due to rounding.

3. FINANCIAL COSTS

The details and methods used in the analysis of financial costs of non-adherence in 2005 are provided in the following sections, with a summary in Table 3-1 of the base case.

TABLE 3-1 FINANCIAL COSTS FOR NON-ADHERENCE WITH BISPHOSPHONATES 2005, $M

	Males	Females	Total
Health system cost	2.1	20.7	22.8
- *Hospital*	0.8	7.7	8.5
- *Residential aged care*	1.1	10.7	11.7
- *Rehabilitation/other*	0.2	2.4	2.6
Medication wastage	4.7	25.1	29.8
Productivity	0.1	0.5	0.6
Informal care	2.8	27.3	30.1
Mobility aids	0.0	0.1	0.1
Real transfer gains	0.0	0.0	0.0
Total financial costs	**9.6**	**73.7**	**83.3**

During 2005, **the total financial costs associated with non-adherence with bisphosphonates are estimated to be $85.9 million.** Informal care generates the most financial costs of non-adherence ($30.1 million), with medication wastage a close second ($29.8 million).

3.1 HEALTH SYSTEM COSTS

Total health system costs are based on work by AIHW (2005a) for the year 2000-01. Given that the reference year for the current analysis is 2005, costs have been projected by 3.2% per annum based on average health cost inflation over the period to 1992-93 to 2002-03 (AIHW, 2005b:10). This is then used to estimate the expected health system cost per person experiencing a non-adherence osteoporotic fracture in 2005.

3.1.1 HOSPITALISATIONS

Average cost of hospitalisation for fracture in 2000-01, as per the AIHW (2005) work, was $4,327 per separation. This may be conservative, in part because of the low proportion of fractures classified as osteoporotic on discharge summaries (Access Economics, 2001). The cost of a hip fracture (the most expensive type of fracture) was estimated from the Dubbo Osteoporosis Epidemiology Study as $23,000 in 2001. However, again in order to adopt a conservative approach where uncertainty exists, the AIHW cost per separation is utilised here. Assuming just one hospitalisation per person in the year of the fracture occurring, and health cost inflation of 3.2% per annum from the baseline to 2005, the average cost of hospitalisation in 2005 was $4,908. Multiplying the average cost by the number of fractures results **in the total hospital costs being $8.5 million in 2005**.

3.1.2 RESIDENTIAL AGED CARE

Access Economics (2005) has undertaken previously separate analysis of the costs of residential aged care for people with osteoporotic fractures using data from the ABS Survey of Disability Ageing and Carers (SDAC). According to the 2003 SDAC the vast majority (84%) of

people with a severe or profound core-activity limitation due to osteoporosis remain living at home, 14% live in nursing home or aged care hostels, while the remaining 2% are in other forms of cared accommodation, including hospitals, hostels for people with disabilities and some cared components of retirement villages. Access Economics previously estimated that the average cost of a residential aged care bed was $44,282 in 2001-02 (Access Economics, 2004). Adjusting for average health cost inflation (3.2% per annum), this would represent an average cost of $48,671 in 2005, **for a total cost of $11.7 million for residential aged care in 2005**. The effect would of course be compounding for subsequent years as many patients would require ongoing care beyond 2005.

3.1.3 REHABILITATION

While not all people who suffer an osteoporotic fracture would require or receive rehabilitation, Access Economics (2005) estimated (possibly conservatively, given the morbidity literature) that 50% of the hospitalisations due to osteoporotic fractures were for people with severe or profound disability from osteoporosis who would generally receive such rehabilitation. On this basis, in the base case around (50%*1,274=) 862 people would need to receive such rehabilitation because of the fractures resulting from non-adherence.

After discharge, patients typically need to follow a program of rehabilitation designed to help the fracture heal and prevent further fractures. Rehabilitation needs may vary considerably between patients and the location of the fracture. Hip fractures require a significantly different rehabilitation plan from non-hip fractures. Based on consultations with a musculoskeletal specialist expert, and assuming that around 20% of all fractures are hip-related, Access Economics (2005) costed an 'average' rehabilitation program for people with all types of osteoporotic fractures discharged from hospital. The average number of medical and allied health rehabilitative services required in the year following the fracture were estimated to cost $3,001 per person in 2005 (Table 3-2).

TABLE 3-2 REHABILITATION COSTS FOR OSTEOPOROTIC FRACTURES, AUSTRALIA, 2005

Number of visits in year following fracture		Unit cost	Annual cost per person
Specialist medical consultations	3	$70	$210
GP consultations	3	$37	$111
Physiotherapy	10	$120	$1,200
Occupational therapy	4	$120	$480
Home nursing	20	$25	$500
Home help	20	$25	$500
Exercise	50	-	
Total			**$3,001**

Note: Numbers may not sum due to rounding.

If half of the estimated non-adherents who are discharged from hospital after a serious osteoporotic fracture followed this rehabilitation program at a cost of just over $3,000 per person, **the estimated total cost of rehabilitation in 2005 was $2.6 million.**

3.2 MEDICATION WASTAGE

Medication wastage comes about because non-adherence has a level of (government) expenditure associated with the dispensing of medication for patients. The current analysis has shown that 40.9% of bisphosphonate users (114,434 people) will not receive the therapeutic benefit of fracture risk reduction for adherence with therapy. The average cost of a

bisphosphonate prescription under the PBS is $55.91. The average number of medications that a patient will use before discontinuing therapy is estimated to be 4.65. **In 2005, it calculated that there was $29.8 million in medication wastage for no therapeutic benefit.**

3.3 PRODUCTIVITY

Access Economics (2001) noted that people with osteoporosis aged 15-64 years participate in the labour force less (with a difference of 1.1%) than the average for people of the same age, primarily due to early retirement of women. It is likely that men and women aged over 65 years with osteoporosis would also participate in the labour force less than those without, and this difference is also approximated as 1.1% of the fractures experienced multiplied by average weekly earnings annualised for men and women aged over 65 years ($30,056 per annum). **The loss of productivity in 2005 for fractures for patients not adhering to bisphosphonate was thus estimated as $570,064.**

3.4 INFORMAL CARE

The 2003 ABS SDAC reported that 35,300 informal primary carers (7.4% of all primary carers) provided care for people with osteoporosis as their main disabling condition. While some types of care provided (eg, health care) were met more by formal care providers, 96.5% of people with a severe or profound core activity limitation from osteoporosis receive some form of informal assistance, with the greatest need being for mobility (see Access Economics, 2005, p42 and Figure 6-2). The value of this informal care can be estimated using either *opportunity cost valuation* (the earnings foregone by people not employed due to their caring responsibilities) as a minimum estimate or *replacement valuation* (the cost of replacing that care with formal sector services if informal care were not available) as an upper bound. These costs, on average, for people with osteoporosis, have been calculated by Access Economics (2005, Tables 6-3 and 6-4) and multiplied by growth in average weekly earnings to give $17,452 as the average annual cost of informal care per fracture in 2005.

These costs, on average, for people with disabling osteoporosis fractures then multiplied by the number of fractures in the non-adhering population to estimate total costs associated with informal care for 2005 for people suffering disabling osteoporotic fractures. **The total value of informal care provided to patients who suffer a osteoporotic fracture because of non-adherence with bisphosphonates in 2005 was $30.1 million.**

3.5 MOBILITY AIDS

SDAC data showed that 60.4% of people with severe osteoporosis will use some form of mobility aid. The most popular aids are walking frames or sticks, which are used by over one-third of people with severe osteoporosis. Around 14% of people with severe osteoporosis use a wheelchair or scooter. The annual average cost of mobility aids used by people with severe osteoporosis is estimated as $62 per person in 2005 (Access Economics, 2005). Multiplied by the number of people with osteoporosis experiencing a fracture because of non-adherence, **the cost of mobility aids in 2005 was $171,000**.

3.6 REAL TRANSFER GAINS

If income and production are lost when an osteoporotic fracture occurs, then associated taxation revenues are also lost. Moreover, people with disability arising from non-adherence to bisphosphonate therapy may receive government income payments drawn from taxation revenue. While these transfers themselves constitute merely a redistribution in financial flows, there are real 'deadweight' efficiency losses caused by the administrative costs and

distortionary impacts from raising taxation revenue to replace that lost and to finance extra government spending. However, these are likely to be so small given the level of economic activity through employment activities among this patient group that they have not been estimated in this analysis.

3.7 SENSITIVITY ANALYSIS

Sensitivity analysis in relation to financial costs, using the higher and lower fracture rates, is presented in Table 3-3.

- With the higher fracture rates (5.2% and 2.8% for females and males respectively), the total financial costs are estimated as $115.5 million.
- With the lower fracture rates (1.3% and 0.7% for females and males respectively), the total financial costs are estimated as $51.2 million.

TABLE 3-3 SCENARIO ANALYSIS, FINANCIAL COSTS OF NON-ADHERENCE, 2005, $M

	Males	Females	Total
High scenario fracture rate	**2.8%**	**5.2%**	
Health system cost	3.3	33.1	36.5
- *Hospital*	1.2	12.3	13.5
- *Residential aged care*	1.7	17.1	18.8
- *Rehabilitation/other*	0.4	3.8	4.1
Medication wastage	4.7	25.1	29.8
Productivity	0.1	0.8	0.9
Informal care	4.4	43.7	48.1
Mobility aids	0.0	0.2	0.2
Real transfer gains	0.0	0.0	0.0
Total financial costs	12.5	102.9	115.5
Low scenario fracture rate	**0.7%**	**1.3%**	
Health system cost	0.8	8.3	9.1
- *Hospital*	0.3	3.1	3.4
- *Residential aged care*	0.4	4.3	4.7
- *Rehabilitation/other*	0.1	0.9	1.0
Medication wastage	4.7	25.1	29.8
Productivity	0.0	0.2	0.2
Informal care	1.1	10.9	12.0
Mobility aids	0.0	0.0	0.0
Real transfer gains	0.0	0.0	0.0
Total financial costs	6.7	44.5	51.2

4. HEALTHY LIFE LOST

4.1 VALUING THE 'BURDEN OF DISEASE'

4.1.1 VALUING LIFE AND HEALTH

Since Schelling's (1968) discussion of the economics of life saving, the health economic literature has properly focused on **willingness to pay** (willingness to accept) measures of mortality and morbidity risk. Using evidence of market trade-offs between risk and money, including numerous labour market and other studies (such as installing smoke detectors, wearing seatbelts or bike helmets etc), economists have developed estimates of the **value of a 'statistical' life (VSL).**

> The willingness to pay approach estimates the value of life in terms of the amounts that individuals are prepared to pay to reduce risks to their lives. It uses stated or revealed preferences to ascertain the value people place on reducing risk to life and reflects the value of intangible elements such as quality of life, health and leisure. While it overcomes the theoretical difficulties of the human capital approach, it involves more empirical difficulties in measurement (BTE, 2000, pp20-21).

Viscusi and Aldy (2002) summarise the extensive literature in this field, most of which has used econometric analysis to value mortality risk and the 'hedonic wage' by estimating compensating differentials for on-the-job risk exposure in labour markets, in other words, determining what dollar amount would be accepted by an individual to induce him/her to increase the possibility of death or morbidity by x%. They find the VSL ranges between US$4 million and US$9 million with a median of US$7 million (in year 2000 US dollars), similar but marginally higher than the VSL derived from US product and housing markets, and also marginally higher than non-US studies, although all in the same order of magnitude. They also review a parallel literature on the implicit value of the risk of non-fatal injuries.

> A particular life may be regarded as priceless, yet relatively low implicit values may be assigned to life because of the distinction between identified and anonymous (or 'statistical') lives. When a 'value of life' estimate is derived, it is not any particular person's life that is valued, but that of an unknown or statistical individual (Bureau of Transport and Regional Economics, 2002, p19).

Weaknesses in this approach, as with human capital, are that there can be substantial variation between individuals. Extraneous influences in labour markets such as imperfect information, income/wealth or power asymmetries can cause difficulty in correctly perceiving the risk or in negotiating an acceptably higher wage.

Viscusi and Aldy (2002) include some Australian studies in their meta-analysis, notably Kniesner and Leeth (1991) of the ABS with VSL[6] of US2000 $4.2 million and Miller et al (1997) of the National Occupational Health and Safety Commission (NOHSC) with quite a high VSL of US2000$11.3m-19.1 million (Viscusi and Aldy, 2002, Table 4, pp92-93). Since there are

[6] Value of the remaining life left for the average person surveyed.

relatively few Australian studies, there is also the issue of converting foreign (US) data to Australian dollars using either exchange rates or purchasing power parity and choosing a period.

Access Economics has previously presented outcomes from Yale University (Nordhaus, 1999) – where VSL is estimated as $US2.66m; University of Chicago (Murphy and Topel, 1999) – US$5m; Cutler and Richardson (1998) – who model a common range from US$3m to US$7m, noting a literature range of $US0.6m to $US13.5m per fatality prevented (1998 US dollars). These studies apply discount rates of 0% and 3% (favouring 3%) to the common range to derive an equivalent of $US 75,000 to $US 150,000 for a year of life gained.

4.1.2 DALYs AND QALYs

In an attempt to overcome some of the issues in relation to placing a dollar value on a human life, in the last decade an alternative approach to valuing human life has been derived. The approach is non-financial, where pain, suffering and premature mortality are measured in terms of Disability Adjusted Life Years (DALYs), with 0 representing a year of perfect health and 1 representing death (the converse of a QALY or "quality-adjusted life year" where 1 represents perfect health). This approach was developed by the World Health Organization, the World Bank and Harvard University and provides a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990, projected to 2020 (Murray and Lopez, 1996). Methods and data sources are detailed further in Murray et al (2001).

The DALY approach has been adopted and applied in Australia by the Australian Institute for Health and Welfare (AIHW) with a separate comprehensive application in Victoria. Mathers et al (1999) from the AIHW estimate the burden of disease and injury in 1996, including separate identification of premature mortality (Years of Life Lost - YLL) and morbidity (Years of Life Lost due to Disability - YLD) components:

$$DALYs = YLLs + YLDs$$

In any year, the disability weight of a disease (for example, 0.18 for a broken wrist) reflects a relative health state. In this example, 0.18 would represent losing 18% of a year of healthy life because of the inflicted injury.

The DALY approach has been successful in avoiding the subjectivity of individual valuation and is capable of overcoming the problem of comparability between individuals and between nations, although nations have subsequently adopted variations in weighting systems. For example, in some countries DALYs are age-weighted for older people although in Australia the minority approach is adopted – valuing a DALY equally for people of all ages.

The main problem with the DALY approach is that it is not financial and is thus not directly comparable with most other cost measures. In public policy making, therefore, there is always the temptation to re-apply a financial measure conversion to ascertain the cost of an injury or fatality or the value of a preventive health intervention. Such financial conversions tend to utilise "willingness to pay" or risk-based labour market studies described above.

The Department of Health and Ageing (based on work by Applied Economics) adopted a very conservative approach to this issue, placing the value of a human life year at around A$60,000 per annum, which is lower than most international lower bounds on the estimate.

> *"In order to convert DALYs into economic benefits, a dollar value per DALY is required. In this study, we follow the standard approach in the economics*

literature and derive the value of a healthy year from the value of life. For example, if the estimated value of life is A$2 million, the average loss of healthy life is 40 years, and the discount rate is 5 per cent per annum, the value of a healthy year would be $118,000.[7] Tolley, Kenkel and Fabian (1994) review the literature on valuing life and life years and conclude that a range of US$70,000 to US$175,000 per life year is reasonable. In a major study of the value of health of the US population, Cutler and Richardson (1997) adopt an average value of US$100,000 in 1990 dollars for a healthy year.

Although there is an extensive international literature on the value of life (Viscusi, 1993), there is little Australian research on this subject. As the Bureau of Transport Economics (BTE) (in BTE, 2000) notes, international research using willingness to pay values usually places the value of life at somewhere between A$1.8 and A$4.3 million. On the other hand, values of life that reflect the present value of output lost (the human capital approach) are usually under $1 million.

The BTE (2000) adopts estimates of $1 million to $1.4 million per fatality, reflecting a 7 per cent and 4 per cent discount rate respectively. The higher figure of $1.4 million is made up of loss of workforce productivity of $540,000, loss of household productivity of $500,000 and loss of quality of life of $319,000. This is an unusual approach that combines human capital and willingness to pay concepts and adds household output to workforce output.

For this study, a value of $1 million and an equivalent value of $60,000 for a healthy year are assumed.[8] In other words, the cost of a DALY is $60,000. This represents a conservative valuation of the estimated willingness to pay values for human life that are used most often in similar studies.[9]" (DHA, 2003, pp11-12)."

As the citation concludes, the estimate of $60,000 per DALY is very low. The Viscusi (1993) meta-analysis reviewed 24 studies with values of a human life ranging between $US 0.5 million and $US 16m, all in pre-1993 US dollars. Even the lowest of these converted to 2003 Australian dollars at current exchange rates, exceeds the estimate adopted ($1m) by nearly 25%. The BTE study tends to disregard the literature at the higher end and also adopts a range (A$1-$1.4m) below the lower bound of the international range that it identifies (A$1.8-$4.3m).

The rationale for adopting these very low estimates is not provided explicitly. Certainly it is in the interests of fiscal restraint to present as low an estimate as possible.

In contrast, the majority of the literature as detailed above appears to support a higher estimate for VSL, as presented in Table 4-1, which Access Economics believes is important to consider in disease costing applications and decisions. The US dollar values of the lower bound, midrange and upper bound are shown in the table. The 'average' estimate is the

[7] *In round numbers, $2,000,000 = $118,000/1.05 + $118,000/(1.05)^2 + … + $118,000/(1.05).*^{40} [Access Economics comment: The actual value should be $116,556, not $118,000 even in round numbers.]

[8] The equivalent value of $60,000 assumes, in broad terms, 40 years of lost life and a discount rate of 5 per cent. [Access Economics comment: More accurately the figure should be $58,278.]

[9] In addition to the cited references in the text, see for example Murphy and Topel's study (1999) on the economic value of medical research. [Access Economics comment. Identical reference to our Murphy and Topel (1999).]

average of the range excluding the high NOHSC outlier. Equal weightings are used for each study as the:

- Viscusi and Aldy meta-analysis summarises 60 recent studies;
- ABS study is Australian; and
- Yale and Harvard studies are based on the conclusions of eminent researchers in the field after conducting literature analysis.

Where there is no low or high US dollar estimate for a study, the midrange estimate is used to calculate the average. The midrange estimates are converted to Australian dollars at purchasing power parity (as this is less volatile than exchange rates) of USD=0.7281AUD for 2003 as estimated by the OECD.

Access Economics concludes the VSL range in Australia lies between $3.7m and $9.6m[10], with a mid-range estimate of $6.5m. These estimates have conservatively not been inflated to 2004 prices, given the uncertainty levels.

TABLE 4-1 INTERNATIONAL ESTIMATES OF VSL, VARIOUS YEARS

	US$m			A$m
	Lower	Midrange	Upper	0.7281
Viscusi and Aldy meta-analysis 2002	4	7	9	**9.6**
Australian: ABS 1991		4.2		5.8
NOHSC 1997	11.3		19.1	
Yale (Nordhaus) 1999		2.66		**3.7**
Harvard (Cutler and Richardson) 1998	0.6	5	13.7	6.9
Average*	2.9	**4.7**	7.4	**6.5**

* Average of range excluding high NOHSC outlier, using midrange if no data; conservatively not inflated.

A$m conversions are at the OECD 2003 PPP rate.

4.1.3 DISCOUNT RATES

Choosing an appropriate discount rate for present valuations in cost analysis is a subject of some debate, and can vary depending on which future income or cost stream is being considered. There is a substantial body of literature, which often provides conflicting advice, on the appropriate mechanism by which costs should be discounted over time, properly taking into account risks, inflation, positive time preference and expected productivity gains.

The absolute minimum option that one can adopt in discounting future income and costs is to set future values in current day dollar terms on the basis of a risk free assessment about the future (that is, assume the future flows are similar to the certain flows attaching to a long term Government bond).

Wages should be assumed to grow in dollar terms according to best estimates for inflation and productivity growth. In selecting discount rates for this project, we have thus settled upon the following as the preferred approach.

- **Positive time preference:** We use the long term nominal bond rate of 5.8% pa (from recent history) as the parameter for this aspect of the discount rate. (If there were no

[10] Calculated from the non-indexed studies themselves. Converting the Access Economics average estimates from USD to AUD at PPP would provide slightly higher estimates - $3.9 million and $10.2m, with the same midrange estimate.

positive time preference, people would be indifferent between having something now or a long way off in the future, so this applies to all flows of goods and services.)

- **Inflation:** The Reserve Bank has a clear mandate to pursue a monetary policy that delivers 2 to 3% inflation over the course of the economic cycle. This is a realistic longer run goal and we therefore endorse the assumption of 2.5% pa for this variable. (It is important to allow for inflation in order to derive a real (rather than nominal) rate.) Health cost inflation, however, has been higher at around 3.2% per annum in recent years according to AIHW data.
- **Productivity growth:** The Commonwealth Government's Intergenerational report assumed productivity growth of 1.7% in the decade to 2010 and 1.75% thereafter. We suggest 1.75% for the purposes of this analysis.

There are then two different discount rates that should be applied:

- To discount income streams of future earnings, the discount rate is:
  5.8 - 2.5 - 1.75 = 1.55%.
- To discount health costs, the discount rate is:
  5.8 - 3.2 = 2.6%.
- To discount other future streams (healthy life) the discount rate is:
  5.8 – 2.5 = 3.3%

While there may be sensible debate about whether health services (or other costs with a high labour component in their costs) should also deduct productivity growth from their discount rate, we argue that these costs grow in real terms over time significantly as a result of other factors such as new technologies and improved quality, and we could reasonably expect this to continue in the future.

Discounting the VSL[11] of $3.7m from Table 4-1 by the discount rate of 3.3% over an average 40 years expected life span (the average from the meta-analysis of wage-risk studies) provides an estimate of the value of a life year of $162,561.

4.1.4 ESTIMATING BURDEN OF DISEASE

Burden of disease is estimated by applying the lower bound value of a statistical life year of $162,561 (based on the lower bound of the value of a statistical life of $3.7 million) to the total Disability Adjusted Life Years (DALYs) due to osteoporotic fractures:

- For each person, YLDs are based on YLDs per incident case from Mathers et al (1999), with a discount rate of 3.3% and no age weighting.
- For each person, YLLs are estimated by multiplying the probability of dying of the consequences of osteoporosis in each year after diagnosis (adjusted by the general mortality rate ie, the probability of dying anyway of some other cause) by the corresponding YLLs for the age of death in the Standard Life Expectancy Table (West Level 26) at a discount rate of 3.3% and no age weighting. YLLs are allocated to the year that the person died.
- YLDs and YLLs are added together to estimate total DALYs.

[11] Value of the remaining life left for the average person surveyed.

- The source studies from which the VSL is drawn implicitly include the individual's net estimation of other personal costs – notably lost earnings (after tax) and out-of-pocket expenses. Thus the net cost of suffering and premature death from the consequences of osteoporosis should exclude these to avoid double counting.

4.2 SUMMARY OF BURDEN OF DISEASE

Ultimately the greatest loss from the impact of non-adherence with bisphosphonate therapy is the resultant burden of disease of the fracture measured in disability adjusted life years (DALYs) including the years of life lost due to premature death (YLL) and the years of healthy life lost due to disability (YLD). One in five people who suffer hip fracture die within six months of sustaining the fracture (Access Economics, 2001, p8). Additional morbidity from osteoporosis can be either symptomatic (eg, pain, deformity) or asymptomatic (eg, fear of falling leading to social isolation, being bed-ridden, anxiety about fracture which can lead to emotional disturbances such as depression and impair activities).

These estimates calculate mortality as 20% of fractures occurring that are likely to be hip fractures (AIHW data report that 36.6% of hospitalised fractures are femoral, but the analysis conservatively models 20% of fractures being hip fractures). This provides the conservative estimate of 'lives lost' as 20% * 20% * 1,724 'excess' fractures (from Table 2-11) = 69 in 2005 – conservative because other types of fracture may also lead to death. It is assumed that fractures causing death shorten life by five years, with a discount rate for healthy life years of 3.3% used to derive the total YLL value of 324 DALYs. Access Economics (2001) calculated the ratio of YLD/YLL as 95.5% which is used here to estimate YLD in 2005 as 494. Using the value of a life year as $162,561 based conservatively on the Australian and international evidence from wage-risk studies using willingness to pay methodology, **the dollar value of the QALYs lost due to non-adherence with bisphosphonates is estimated as $102.8 million in 2005.** In the high scenario the value of the healthy life lost is estimated as $164.5 million while in the low scenario it is estimated as $41.1 million.

TABLE 4-2 BURDEN OF DISEASE FROM NON-ADHERENCE WITH BISPHOSPHONATES IN 2005

	Males	Females	Total
Base case			
Lives lost	6	63	69
Life years lost (YLL)	30	294	324
Years life lost to disability (YLD)	28	281	309
QALYs	58	575	632
Quality of life lost ($m)	9.4	93.4	102.8
High scenario			
Lives lost	10	100	110
Life years lost (YLL)	47	470	518
Years life lost to disability (YLD)	45	449	494
QALYs	93	919	1012
Quality of life lost ($m)	15.1	149.4	164.5
Low scenario			
Lives lost	3	25	28
Life years lost (YLL)	12	118	129
Years life lost to disability (YLD)	11	112	124
QALYs	23	230	253
Quality of life lost ($m)	3.8	37.4	41.1

Note: Numbers may not sum due to rounding.

5. PROJECTIONS

The analysis so far has been prevalence-based for the year 2005, representing a snapshot of the problem of adherence to bisphosphonate treatment of osteoporosis. Many people with osteoporosis have not persisted with therapy in previous years and many new patients will not persist with therapy in the future with an increasing degree of fragility over time. In this section, the present value of future economic costs is estimated.

5.1 METHODOLOGY

Costs from bisphosphonate non-adherence were projected to 2010 on the following basis.

- The number of Australians each year taking bisphosphonates was projected to increase, *ceteris paribus*, from the number estimated in 2005 (235,680) by the growth in the population aged 65 years and over, based on ABS demographic projections, calculated separately for males (16.3% growth by 2010) and females (12.2%).
- The number of people not adhering each year was projected as 40.9% of the number taking bisphosphonates, and the number of ineffective treatments was projected as 4.65 times the number not adhering, based on the PBS data that showed that non-adherents received on average 4.65 dispensed medications during the 12 months (Section 2.3.2).
- The number of projected fractures each year due to bisphosphonate non-adherence was derived as half of the fracture rate multiplied by the number not adhering.
- Health system costs were projected as the sum of hospital, residential and rehabilitation cost components with:
  - hospital and rehabilitation costs calculated as the number of fractures in each year multiplied by average hospital and rehabilitation costs respectively inflated each year by the average health cost inflator from recent history of 3.2% per annum; and
  - residential aged care costs calculated as the number of fractures in each year, cumulative for three years (the expected length of stay), with costs per person also inflated each year by the health cost inflator.
- Medication wastage costs were projected as the number of ineffective treatments each year multiplied by the average cost of a treatment, which was inflated by forecast growth in the Consumer Price Index (estimated from the Access Economics Macroeconomic model).
- Productivity costs were projected as the fractures due to non-adherence cumulative for three years (the expected years to retirement), multiplied by 1.1% of average annual earnings, which was inflated by forecast growth in Average Weekly Earnings (estimated from the Access Economics Macroeconomic model).
- Informal care costs were projected as the fractures due to non-adherence cumulative for three years (the expected years to institutionalisation, recovery or death), multiplied by the average cost per annum of informal care, which was also inflated by forecast growth in Average Weekly Earnings.
- The cost of mobility aids was projected as the fractures due to non-adherence cumulative for three years (the expected years the aid would be required), multiplied by the average cost per annum of such aids, which was inflated by forecast growth in the Consumer Price Index.

- The lives lost each year due to non-adherence was calculated as the fractures due to non-adherence multiplied by 20% (mortality rate) of 20% (hip fractures), with the years of life lost calculated as the discounted stream over five years at a 3.3% per annum discount rate. The associated years of healthy life lost due to disability from the non-adherence fractures (the disability burden) was calculated as 95.5% of the mortality burden, and the sum of these as the total DALYs lost. This in turn was multiplied by the value of a life year to estimate the dollar value of the burden of disease from non-adherence fractures.
- Over the period, the net present value (NPV) of each cost stream was calculated by discounting each nominal projection cumulatively by 5.8% per annum.

5.2 FINDINGS

Results are presented in Table 5-1, showing 10,950 fractures due to non-adherence in the base case over the six years, with a NPV of $1.7 billion ($0.8 billion to $2.6 billion) of which $1.0 billion ($0.5 billion to $1.5 billion) is the NPV of the financial costs and $647 million ($259 million to $1.0 billion) is the NPV of the value of the healthy life lost.

TABLE 5-1 PROJECTED FRACTURES AND COSTS: BASE, HIGH AND LOW SCENARIOS, 2005-2010

	2005	2006	2007	2008	2009	2010	NPV*
Base case							
Fractures due to non-adherence	1,724	1,760	1,799	1,838	1,887	1,941	10,950
Health system costs ($m)	22.8	36.1	50.6	53.4	56.4	59.8	276.9
- Hospital	8.5	8.9	9.4	9.9	10.5	11.2	57.8
- Residential aged care	11.7	24.5	38.3	40.4	42.7	45.2	201.4
- Rehabilitation/other	2.6	2.7	2.9	3.0	3.2	3.4	17.7
Medication wastage	29.8	31.4	32.9	34.4	36.1	37.9	200.6
Productivity ($m)	0.6	1.2	1.9	2.0	2.2	2.3	10.2
Informal care ($m)	30.1	63.5	100.8	108.0	115.2	122.7	536.5
Mobility aids ($m)	0.1	0.2	0.3	0.4	0.4	0.4	1.8
Total financial costs ($m)	**83.3**	**132.5**	**186.6**	**198.2**	**210.2**	**223.1**	**1,025.9**
Lives lost (no of women)	69	70	72	74	75	78	434
Life years lost (YLL)	324	330	337	345	354	364	2,035
Disability years lost (years)	309	315	322	329	338	348	1,943
DALYs lost (QALYs)	632	646	660	674	692	712	3,978
Quality of life lost ($m)	**102.8**	**104.9**	**107.2**	**109.6**	**112.5**	**115.7**	**646.7**
Total financial and QoL lost ($m)	**186.1**	**237.4**	**293.8**	**307.8**	**322.8**	**338.9**	**1,672.7**
High scenario							
Fractures due to non-adherence	2,759	2,816	2,878	2,941	3,020	3,106	17,519
Health system costs ($m)	36.5	57.8	81.0	85.4	90.3	95.6	443.1
Total financial costs ($m)	**115.5**	**193.1**	**278.8**	**296.4**	**314.7**	**334.2**	**1,521.2**
DALYs lost (QALYs)	1,012	1,033	1,056	1,079	1,108	1,139	6,365
Quality of life lost ($m)	**164.5**	**167.9**	**171.6**	**175.4**	**180.1**	**185.2**	**1,034.8**
Total financial and QoL lost ($m)	**280.0**	**361.0**	**450.4**	**471.8**	**494.8**	**519.4**	**2,555.9**
Low scenario							
Fractures due to non-adherence	690	704	719	735	755	776	4,380
Health system costs ($m)	9.1	14.5	20.2	21.3	22.6	23.9	110.8
Total financial costs ($m)	**51.2**	**71.8**	**94.4**	**99.9**	**105.8**	**112.0**	**530.7**
DALYs lost (QALYs)	253	258	264	270	277	285	1,591
Quality of life lost ($m)	**41.1**	**42.0**	**42.9**	**43.8**	**45.0**	**46.3**	**258.7**
Total financial and QoL lost ($m)	**92.3**	**113.8**	**137.3**	**143.7**	**150.8**	**158.3**	**789.4**

* Note: NPV is lower than the horizontal sum of nominal annual savings due to discounting.

Figure 5-1 and Figure 5-2 illustrate the base, high and low scenarios by year, for fractures and costs of non-adherence.

FIGURE 5-1 PROJECTED FRACTURES AND COSTS: BASE, HIGH AND LOW SCENARIOS, 2005-2010

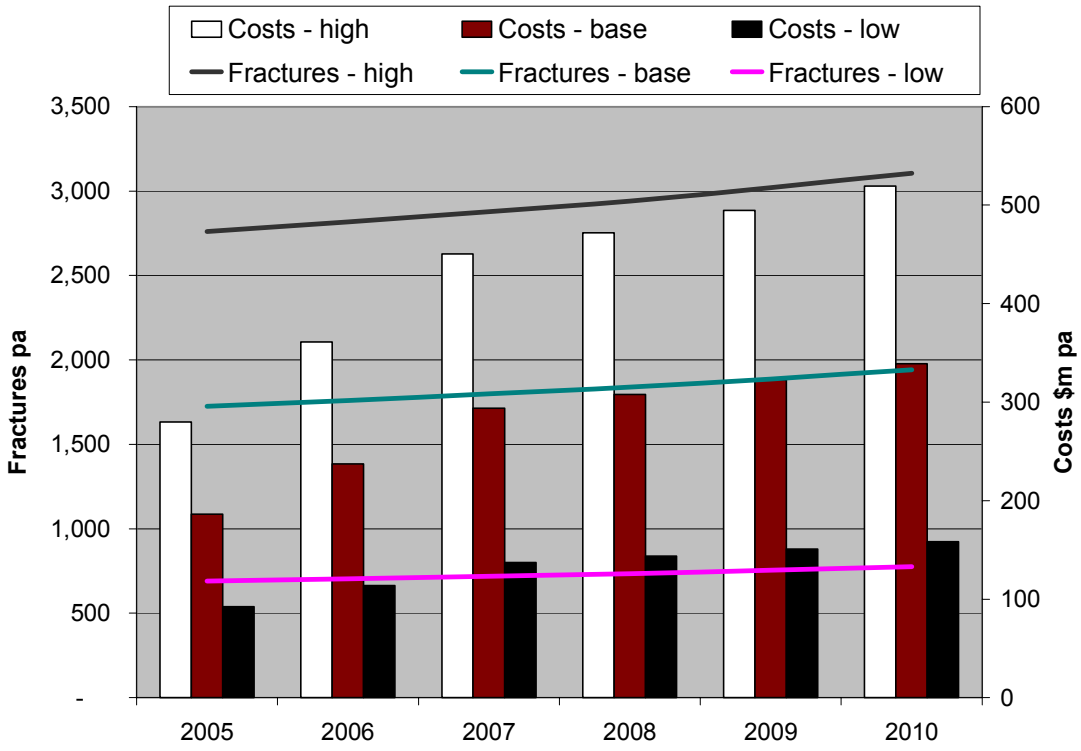
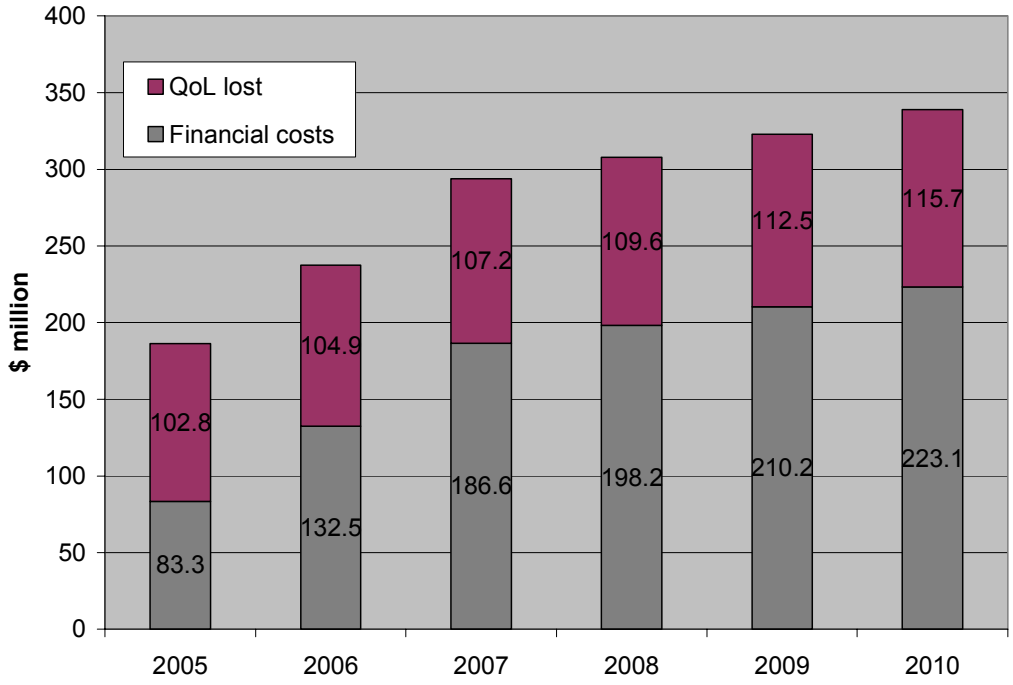


FIGURE 5-2 FINANCIAL AND QUALITY OF LIFE COSTS PROJECTED, BASE CASE, 2005-2010



The increase in financial costs is steepest in the first three years due to the cumulative aspects of some costs of non-adherence fractures, notably residential aged care, informal care, productivity losses and mobility aids.

6. CONCLUSION

In the treatment of osteoporosis, the currently available bisphosphonates are effective yet their utility is compromised by issues of non-adherence with therapy (Miller, 2005). The current analysis (Table 5-1) has shown that **non-adherence with therapy is 40.9% of patients currently using bisphosphonates, which cost an estimated $186.1 million ($92.3-$280.0 million)** in 2005 in total economic costs (financial and wellbeing costs).

TABLE 6-1 ECONOMIC IMPACT OF NON-ADHERENCE WITH BISPHOSPHONATE THERAPY 2005

	Males	Females	Total
Health system cost ($m)	2.1	20.7	22.8
- *Hospital* ($m)	0.8	7.7	8.5
- *Residential aged care* ($m)	1.1	10.7	11.7
- *Rehabilitation/other* ($m)	0.2	2.4	2.6
Medication wastage ($m)	4.7	25.1	29.8
Productivity ($m)	0.1	0.5	0.6
Informal care ($m)	2.8	27.3	30.1
Mobility aids ($m)	0.0	0.1	0.1
Real transfer gains ($m)	0.0	0.0	0.0
Total financial costs ($m)	**9.6**	**73.7**	**83.3**
Lives lost	6	63	69
Life years lost (YLL)	30	294	324
Years life lost to disability (YLD)	28	281	309
QALYs	58	575	632
Quality of life lost ($m)	**9.4**	**93.4**	**102.8**
Total financial & QOL cost ($m)	**19.0**	**167.1**	**186.1**
Total cost ($m) high scenario	**27.6**	**252.4**	**280.0**
Total cost ($m) low scenario	**10.4**	**81.9**	**92.3**

Note: Numbers may not sum due to rounding.

Over 2005-2010, there are projected to be 10,950 fractures due to non-adherence in the base case, with a NPV of $1.7 billion ($0.8 billion to $2.6 billion) of which $1.0 billion ($0.5 billion to $1.5 billion) is the NPV of the financial costs and $647 million ($259 million to $1.0 billion) is the NPV of the value of the healthy life lost.

It is also important to consider that osteoporosis is not unique in poor adherence with therapy. With increasing numbers of efficacious self-administered treatments, the need is apparent for better understanding and management of non-adherence in medications. Effective ways to help people follow medical treatments could have far larger effects on health care than any individual treatment (McDonald et al, 2002).

Reducing oral bisphosphonate dosing frequency has been one measure available to increase therapy convenience and practicality, with the hope of improving compliance and persistence (Cramer et al, 2005; Reginster et al, 2006a; Reid, 2006). There is evidence to suggest that less frequent administration may enhance patient convenience and therapy adherence, and therefore, therapeutic outcome. A review of dosing regimens and adherence by Claxton et al (2001), concluded that once or twice a day regimens had better adherence (about 70%) than those in which patients had to take medicines three or four times a day. In the case of osteoporosis, the current analysis and data from other studies (Cramer and Silverman, 2006;

Reginster et al, 2006b) have shown that weekly dosing improves adherence compared with daily administration. Most recently, the PERSIST study demonstrated that persistence on treatment was increased in patients receiving a once-monthly bisphosphonate plus patient support (56.6%) compared with a once-weekly bisphosphonate (38.6%) after six months (Cooper et al, 2006). However, the levels of adherence and therefore the therapeutic benefit are still sub-optimal. Moreover, some of the failure of treatment initiations may relate to patient and doctor's reluctance to start a regimen that still requires so much care and thought, and once-monthly dosing may be less challenging.

The majority of discontinuers discontinue after the first prescription, and potentially every patient is liable to discontinue treatment even after a long period of regular dosing. Thus, acceptance of therapy is crucial for long-term persistence and every person receiving therapy for osteoporosis needs regular reinforcement of the importance of continuation (Cramer and Silverman, 2006). Measures to improve adherence might include improved physician/patient communication, close monitoring and early intervention in declining adherence (Reginster, 2006). Another approach is strengthening of patient commitment through reinforcement of the connection between treatment response and quality of life benefits. Improved adherence with osteoporosis treatment requires that treatment side effects be minimised and patients are informed of the biological markers that show bone strength and reduction in fragility (Tosteson et al, 2003). However, more research is necessary in this area.

Although there is still a large undetected level of osteoporosis in the population, over the past five years there has been an improvement in its detection. The increase in bisphosphonate use over the period has also increased accordingly, although many of their benefits are not likely being realised because of adherence issues. It is misleading to think that because a patient has been identified with osteoporosis and has been prescribed a bisphosphonate that the therapeutic benefit has been realised. While recognition that simplified dosing regimens and reduced frequency of administration are important factors for improving adherence with therapy, it is only through a combination of factors that the benefits of bisphosphonates on fracture risk reduction will be achieved.

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