Technical Report 2:

An analysis of the utilisation and expenditure of medicines dispensed for the prophylaxis and treatment of osteoporosis

Technical report to NCAOP/HSE/DOHC

By

National Centre for Pharmacoeconomics

An analysis of the utilisation and expenditure of medicines dispensed for the prophylaxis and treatment of osteoporosis

February **2007** **National Centre for Pharmacoeconomics**

Executive Summary

1. The number of prescriptions for the treatment and prophylaxis of osteoporosis has increased from 143,261 to 415,656 on the GMS scheme and from 52,452 to 136,547 on the DP scheme over the time period 2002 to 2005.

2. In 2005 over 60,000 patients received medications for the prophylaxis and treatment of osteoporosis on the GMS scheme with an associated expenditure of €16,093,676.

3. Approximately 80% of all patients who were dispensed drugs for the management of osteoporosis were prescribed either Alendronate (Fosamax once weekly) or Risedronate (Actonel once weekly) respectively.

4. On the DP scheme, over 27,000 patients received medications for the prophylaxis and treatment of osteoporosis in 2005 with an associated expenditure of € 6,028,925.

5. The majority of patients treated with drugs affecting bone structure were over 70 years e.g. 12,224 between 70 and 74yrs and 25,518 over 75yrs.

6. In relation to changes in treatment it was identified from the study that approximately 8% of all patients who are initiated on one treatment for osteoporosis are later switched to another therapy.

7. There was a statistically significant difference between the use of any osteoporosis medication and duration of prednisolone (dose response, chi-square test, $p<0.0001$). The study identified that the longer a patient was prescribed prednisolone the increased likelihood of subsequently being prescribed a bisphosphonate. Of concern however is the fact that over 50% of patients did not receive prophylaxis despite 12 months treatment with prednisolone doses > 7.5mg daily.

8. There were low levels of co-prescribing with potentially interacting drugs. In the majority of cases the co-prescribing rate was less than **2.5%** indicating good prescribing practice in the community setting.

9. A further study on the osteoporosis preparations which quantified co-prescribing with proton pump inhibitors found levels of co-prescribing at **22%.**

10. There were 606 prescriptions for Teriparatide on the High Tech Drug scheme in 2005 with an associated expenditure of € 1,986,061. Approximately 74% of the prescriptions were for the over 70s age group.

11. There were similar patterns of prescribing of osteoporosis drugs between the different healthboard regions. When the results were standardised to the GMS eligible population for each of the healthboard regions it was identified that the greatest consumption of osteoporosis agents occurs predominantly in the Eastern and Southern healthboard regions while the lowest consumption of osteoporosis preparations per 1000 GMS eligible population occurs in the North Western and Midland healthboard region.

This analysis of the utilisation and expenditure of medicines dispensed for the prophylaxis and treatment of osteoporosis had the following aims:

1. To determine the utilisation and expenditure of the different drug groups including the bisphosphonates, calcitriol, calcitonin, strontium, raloxifene and tibolone.
   - Parameters such as prescribing frequency, trends, dose and duration of treatment were determined
   - We also determined what proportion of patients are switched from one treatment to an alternative.
   - For the individual drug groups the agents will be ranked in terms of prescribing frequency and associated expenditure.

2. The prescribing frequency of calcium/vitamin D supplementation as an adjunct in the treatment of osteoporosis is outlined.

3. An analysis of the prescribing of oral corticosteroids, particularly doses of prednisolone greater than 7.5mg per day for a duration exceeding 3 months, was conducted. Co-prescribing of recognised treatments for osteoporosis will be determined.

4. Potential drug interactions involving medications for the prophylaxis and treatment of osteoporosis are highlighted e.g. co-prescribing with anticonvulsants, diuretics, tetracyclines and high cost medicines such as proton pump inhibitors.

5. The High Tech Drugs scheme is analysed to provide information in relation to the prescribing of teripatatide for the treatment of osteoporosis.

6. Regional differences in the prescribing of medicines for prophylaxis and treatment of osteoporosis are outlined.

7. The prescribing patterns are determined for 2004/2005.

Introduction

Osteoporosis is a skeletal disease characterised by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and therefore increased risk of fracture[1]. It occurs predominantly in postmenopausal women and in patients who are taking long-term oral corticosteroids (glucocorticosteroids)[2]. Other factors which increase the risk of developing osteoporosis are low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis and early menopause.

Osteoporosis is a major public health concern because of the potentially devastating results including the increased risk of fractures. In women, the one in six lifetime risk of hip fracture is greater than the one in nine risk of developing breast cancer[3]. Fractures of the hip, vertebral body, and distal forearm have generally been considered as the typical osteoporotic fractures however prospective studies have demonstrated that there is an increased risk of almost all types of fracture in patients with low bone density[4]

Advances in medical technologies have resulted in increased life expectancies and the elderly population now account for the fastest growing age-group worldwide, and the yearly number of fractures is expected to increase substantially with continued aging of the population. The estimated number of hip fractures worldwide is expected to increase from 1.7 million in 1990 to 6.3 million in 2050. The combined annual costs of all osteoporotic fractures have been estimated to be in the region of $20 billion in the USA and about $30 billion in the European Union[1]

Management of patients with Osteoporosis

Bisphosphonates (e.g. Alendronic acid, disodium etidronate, and risedronate, ibandronic acid)

The Bisphosphonates are effective in preventing postmenopausal osteoporosis. Their mode of action is to reduce osteoclast activity and increase osteoclast apoptosis. This action results in more time for secondary mineralisation and therefore increases the mechanical resistance of bone[5]. The optimum duration of treatment has not yet been established. Alendronate has been used safely for up to 10 years, risedronate up to 7 years. Patients prescribed bisphosphonates must have vitamin D supplements where there is underlying deficiency. Some of the bisphosphonates now contain vit D in combination such as fosavance which offers patients alendronate combined with vit D. In a 12-month head-to-head trial involving 1053 patients from 78 U.S sites once-weekly alendronate 70mg and once weekly risedronate 35mg were compared. Greater gains in bone mineral density BMD and greater reductions in markers of bone turnover were seen with alendronate compared with risedronate with similar tolerability [6].

Postmenopausal osteoporosis

Treatments licensed for the management of patients with postmenopausal osteoporosis include calcitriol, calcitonin, raloxifene, strontium ranelate and teriparatide.

Calcium and Vit D

Calcium and vit D may not be effective monotherapy in preventing osteoporotic fractures, except in institutionalised elderly people [7, 8]. Calcium and vit D supplements should therefore be prescribed with other treatments for osteoporosis.

Strontium ranelate

Strontium ranelate reduces the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis. The efficacy of strontium ranelate in reducing the risk of fractures makes it an alternative first line option to alendronate or

risedronate [9] particularly in patients for whom these drugs are not well tolerated or are contraindicated.

Raloxifene

Raloxifene reduces the risk of vertebral fractures and also has been shown to prevent fractures at other sites[10]. It protects against breast cancer and can be regarded as a second line option in younger postmenopausal women with vertebral osteoporosis.

Teriparatide

Teriparatide (Forsteo) (recombinant 1-34 parathyroid hormone), given as a subcutaneous daily injection of 20ug, reduces the risk of both vertebral and non-vertebral fractures in postmenopausal women with osteoporosis[11]. Teriparatide is more expensive than other options and is therefore prescribed to patients with severe osteoporosis who are unable to tolerate or who are unresponsive to other treatments.It is reimbursed under the High Tech Drug scheme.

Hormone replacement therapy

Because the risk-benefit balance of hormone replacement therapy is generally unfavourable in older postmenopausal women, it is regarded as a second line treatment option. It is considered an appropriate option in younger postmenopausal women at high risk of fracture, particularly those with vasomotor symptoms. However with aging, the risks of HRT can outweigh the benefits. Also, HRT would not generally be used to relieve menopausal symptoms for more than four or five years which may not be long enough a duration of therapy to prevent osteoporotic fractures.

Methods

The General Medical Services (GMS) scheme provides free healthcare to approximately 30% of the Irish population. Eligibility is means tested, and confined to persons " who are unable without undue hardship to arrange general practioner services for themselves and their dependants". The service was made available to everyone over 70 years of age from July 2001. The GMS population cannot be considered representative of the entire population as the elderly, the young and the socially disadvantaged are over-represented.

The National Centre for Pharmacoeconomics (NCPE) receives prescription data relating to the Long Term Illness Scheme, the Drug Payments Scheme and the General Medical Services (GMS) Scheme from the GMS Payments Board.
The GMS database was used to identify utilisation and expenditure of all drugs used in the management of osteoporosis on the GMS between January 2004 and December 2005.

All prescriptions under the GMS are aggregated into monthly files for each of the healthboard areas. Each row of data contains details on one prescription item. These details include:-

- The ATC code (a seven digit figure) assigned to the drug.
- The GMS code.
- Some demographic details such as age and gender.
- It also contains the patient's medical card number, the prescribing doctor's number, pharmacy number.
- In relation to the medication prescribed it contains the number of dosage units dispensed, the pharmacist fee, the cost of the prescription and VAT on the cost.

A second file which is called the ‘DMA’ file is also received from the GMS Payments board. This file contains additional data specific to the medications prescribed.
The common link with the GMS file and the DMA file is the GMS code which can be used to join the two files together. The DMA file also contains information on the strength, formulation, number of Defined Daily Doses (DDDs), trade name and pack size of each of the prescriptions made.

All prescription data related to drugs used in the management of osteoporosis was identified for the previous healthboard regions of Ireland (all prescriptions within the three healthboards in the ERHA are aggregated into one) between January 2004 and December 2005.

The osteoporosis drugs are coded using the WHO Anatomic Therapeutic Chemical (ATC) classification and Defined Daily Dose (DDD) is used as the unit of measurement of consumption. DDD is the assumed average maintenance dose per day for a drug used for its main therapeutic indication in adults. The results are standardised for the GMS eligible population for each year to account for changes in the GMS population during the study period and in this case results are expressed in Defined Daily Doses per 1000 GMS population (DID).
Where analysis is carried out at healthboard level results are standardised to the GMS eligible population for each individual healthboard for that year.

Both JMP-In and SAS software packages were used to analyse the data.

Results:

Total no of prescriptions issued for drugs used in the treatment of bone disease on the GMS scheme between 2002 and 2005 [12].

General Medical Services Scheme (GMS)

ATC M05	Drugs for the treatment of bone disease	no of prescriptions	% of total
	2002	143,261	0.48
	2003	225,438	0.7
	2004	320,466	0.91
	2005	415,656	1.11

Total ingredient cost of drugs prescribed for the treatment of bone disease on the GMS scheme between 2002 and 2005 [12].

ATC M05	Drugs for the treatment of bone disease	ingredient cost	% of total
	2002	5,273,304	1.22
	2003	8,200,544	1.59
	2004	11,610,903	1.94
	2005	15,081,509	2.27

Total no of prescriptions issued for drugs used in the treatment of bone disease on the DP scheme between 2002 and 2005[12].

Drug Payments Scheme (DPS)

ATC M05	Drugs for the treatment of bone disease	no of prescriptions	% of total
	2002	52,452	0.58
	2003	78,927	0.85
	2004	108,212	1.09
	2005	136,547	1.29

Total ingredient cost of drugs prescribed for the treatment of bone disease on the DP scheme between 2002 and 2005 [12].

ATC M05	Drugs for the treatment of bone disease	ingredient cost	% of total
	2002	1,920,841	1.11
	2003	2,857,119	1.51
	2004	3,905,148	1.84
	2005	4,991,118	2.14

Both the number of prescriptions and the ingredient cost of drugs prescribed in the management of osteoporosis have increased three fold on the GMS scheme and on the DP scheme between 2002 and 2005

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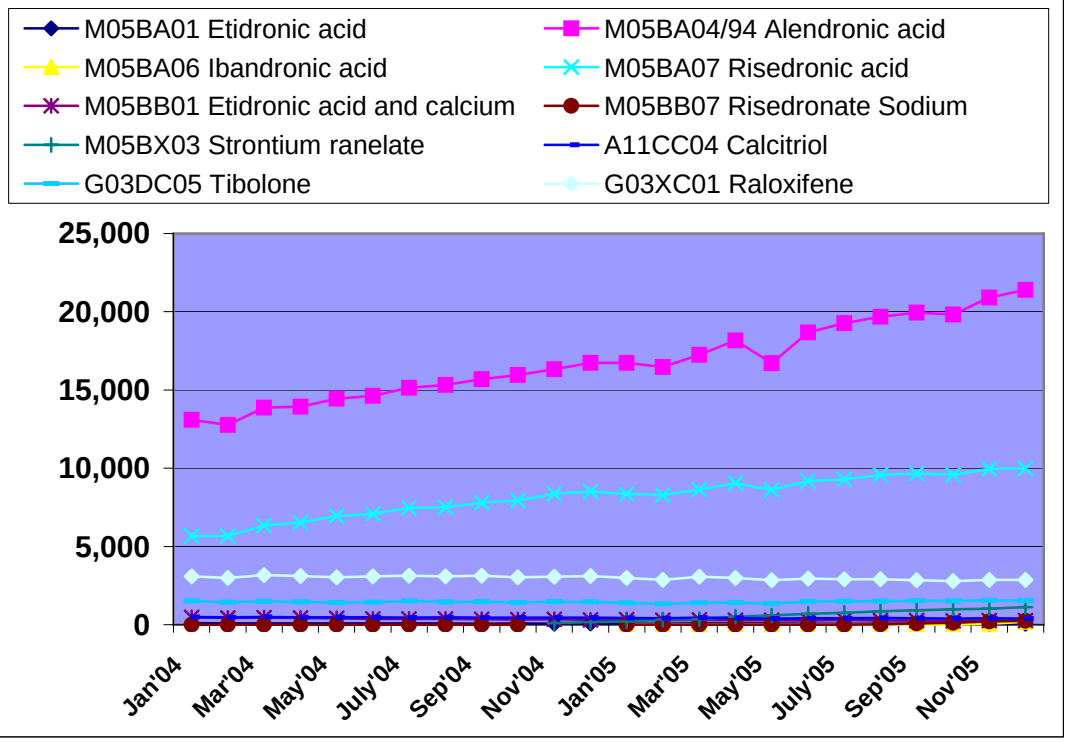
Price of the different preparations of drugs used in the management of osteoporosis as per The Irish Monthly Index of Medicines (MIMS) June 2006.

ATC Drug name	strength	Pack size	Price per pack	Price per tablet
M05BB01 Didronel PMO	400mg	1 x 3 month pack	€ 64.63	€ 21.54 per month
M05BA01 Didronel	200mg	60	€ 66.30	€1.106
M05BA04 Fosamax once weekly	70mg	4	€ 35.26	€ 8.815
M05BA04 Fosamax	10mg	28	€32.64	€ 1.165
M05BA94 Fosavance	70mg	4	€34.64	€ 8.66
M05BA06 Bonviva	150mg	1	€ 32.62	€ 32.62
M05BA07 Actonel	30mg	28	€ 233.40	€ 8.335
M05BA07 Actonel once weekly	35mg	4	€ 36.28	€ 9.07
M05BB07 Actonel combi	32.5mg	1	€ 41.01	€ 41.01
M05BX03 Protelos grans	2g	28	€ 46.13	€ 1.647
G03DC05 Livial	2.5mg	28	€ 17.81	€ 0.636
G03XC01 Evista	60mg	84	€ 89.67	€1.0675

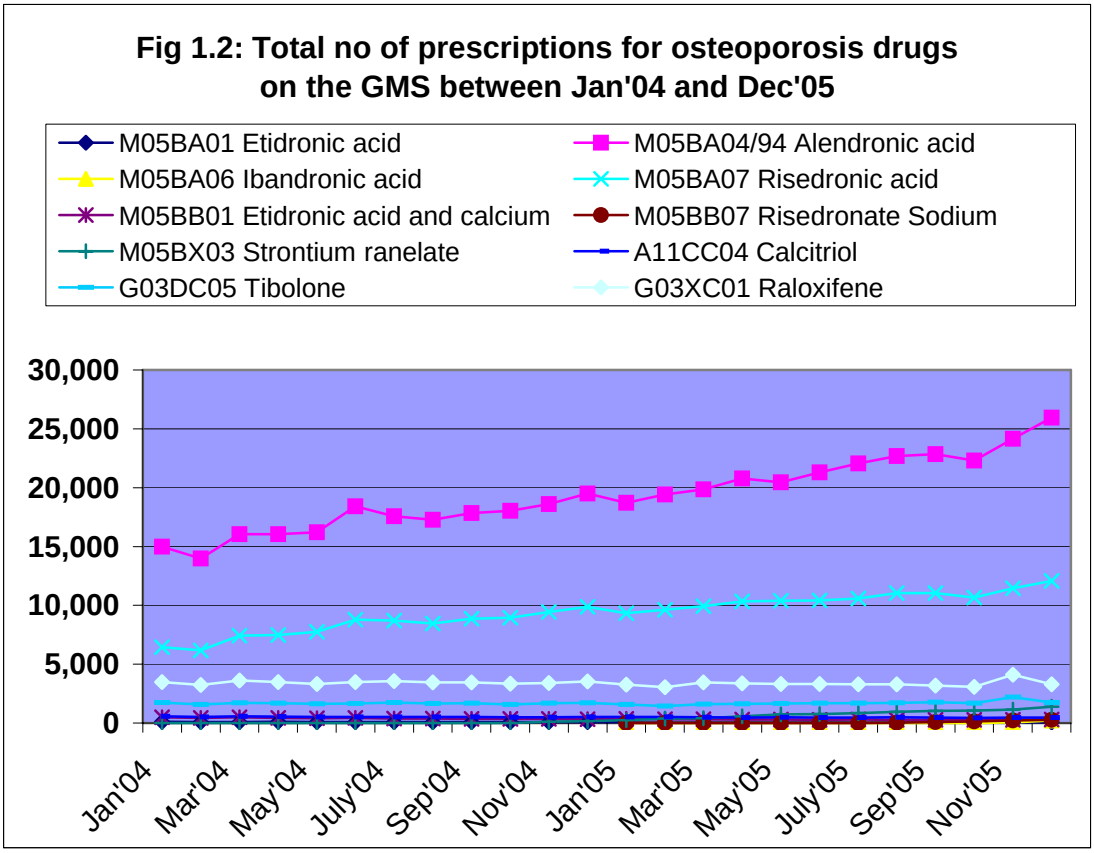
Results from the GMS data:

Fig. 1.1:Total no of patients prescribed medications on the GMS for the management of osteoporosis between Jan'04 and Dec'05



Total no of patients prescribed preparations on the GMS scheme for the management of osteoporosis between 2004 and 2005

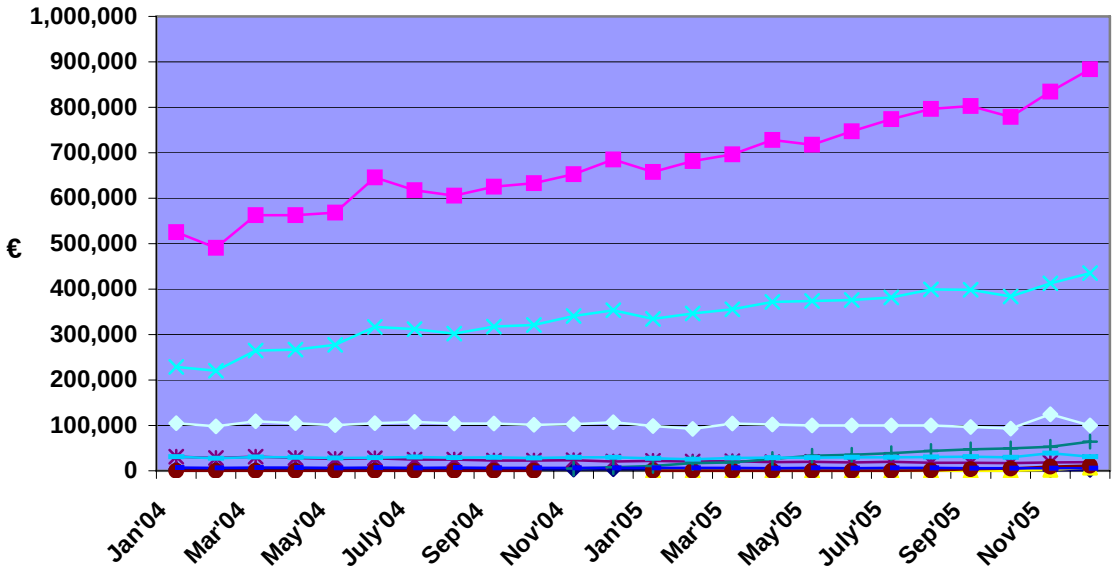
	2004		2005	
ATC	**patients**	**% of total**	**patients**	**% of total**
M05BA01 Etidronic acid	222	0%	173	0%
M05BA04/94 Alendronic acid	27,309	52%	32,615	54%
M05BA06 Ibandronic acid		0%	197	0%
M05BA07 Risedronic acid	14,404	27%	15,568	26%
M05BB01 Etidronic acid and calcium	1,572	3%	1,051	2%
M05BB07 Risedronate Sodium		0%	315	1%
M05BX03 Strontium ranelate	218	0%	2,283	4%
A11CC04 Calcitriol	763	1%	678	1%
G03DC05 Tibolone	2,968	6%	3,014	5%
G03XC01 Raloxifene	4,941	9%	4,498	7%
	52,397	**100%**	**60,392**	**100%**



Total no of prescriptions for osteoporosis drugs on the GMS scheme between 2004 and 2005

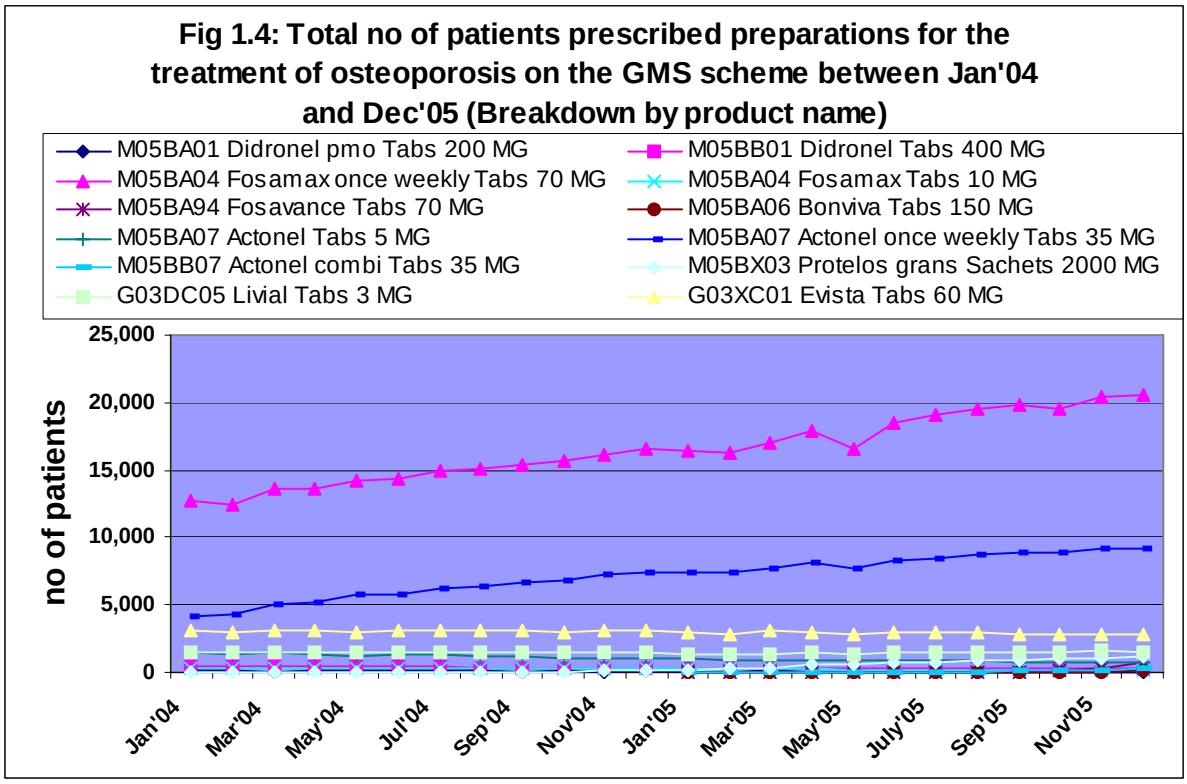
	2004		2005	
ATC	**Prescs**	**% of total**	**Prescs**	**% of total**
M05BA01 Etidronic acid	1,051	0%	841	0%
M05BA04/94 Alendronic acid	204,481	54%	260,512	56%
M05BA06 Ibandronic acid		0%	274	0%
M05BA07 Risedronic acid	98,367	26%	126,882	27%
M05BB01 Etidronic acid and calcium	4,800	1%	3,557	1%
M05BB07 Risedronate Sodium		0%	736	0%
M05BX03 Strontium ranelate	285	0%	9,520	2%
A11CC04 Calcitriol	6,299	2%	5,709	1%
G03DC05 Tibolone	20,062	5%	20,392	4%
G03XC01 Raloxifene	41,399	11%	39,990	9%
	376,744	**100%**	**468,413**	**100%**

Fig 1.3: Total ingredient cost of all drugs prescribed for osteoporosis on the GMS between Jan'04 and Dec'05



Total ingredient cost for osteoporosis drugs on the GMS scheme for the years ended 2004 and 2005

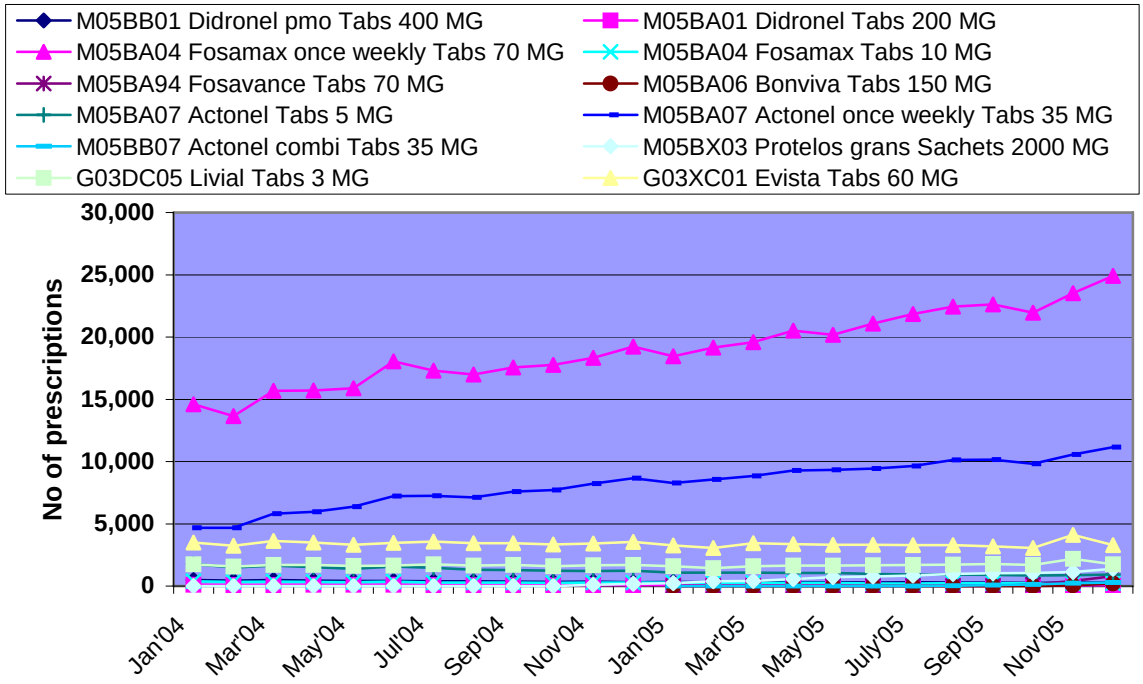
	2004		2005	
ATC	**Ing Cost**	**% of total**	**Ing Cost**	**% of total**
M05BA01 Etidronic acid	39,851	0%	31,916	0%
M05BA04/94 Alendronic acid	7,174,828	56%	9,144,348	57%
M05BA06 Ibandronic acid		0%	8,905	0%
M05BA07 Risedronic acid	3,522,611	28%	4,570,157	28%
M05BB01 Etidronic acid and calcium	310,211	2%	230,018	1%
M05BB07 Risedronate Sodium		0%	29,677	0%
M05BX03 Strontium ranelate	13,032	0%	436,715	3%
A11CC04 Calcitriol	81,161	1%	72,345	0%
A12AX91 Calcium				
G03DC05 Tibolone	351,500	3%	358,691	2%
G03XC01 Raloxifene	1,250,502	10%	1,210,904	8%
	12,743,695	**100%**	**16,093,676**	**100%**



Total no of patients prescribed preparations for the treatment of osteoporosis on the GMS scheme for the years ended 2004 and 2005.

ATC	2,004		2,005	
	patients	% of total	patients	% of total
M05BB01 Didronel PMO	1,492	3%	1,051	2%
M05BA01 Didronel	211	0%	173	0%
M05BA04 Fosamax once weekly	25,130	51%	31,233	52%
M05BA04 Fosamax	674	1%	604	1%
M05BA94 Fosavance		0%	778	1%
M05BA06 Bonviva		0%	197	0%
M05BA07 Actonel	2,349	5%	1,529	3%
M05BA07 Actonel once weekly	11,370	23%	14,039	23%
M05BB07 Actonel combi		0%	315	1%
M05BX03 Protelos grans	218	0%	2,283	4%
G03DC05 Livial	2,968	6%	3,056	5%
G03XC01 Evista	4,941	10%	4,498	8%
	49,353	**100%**	**59,756**	**100%**

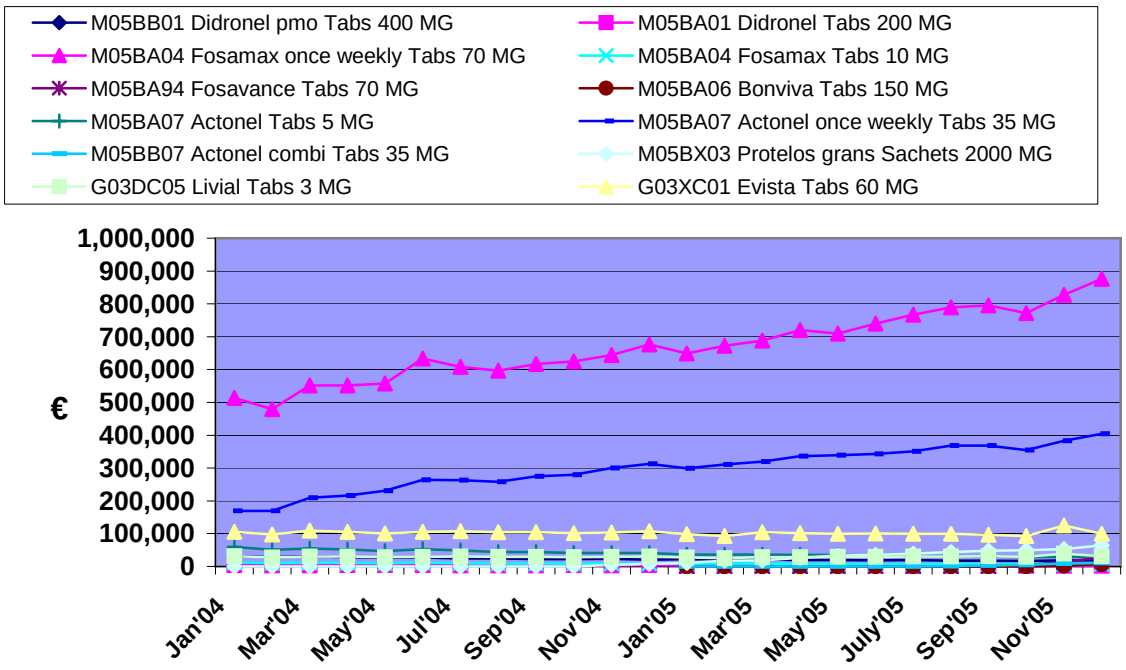
Fig 1.5:Total no of prescriptions for osteoporosis preparations on the GMS between Jan'04 and Dec'05 (Breakdown by product name)



Total no of prescriptions for osteoporosis preparations on the GMS for the years ended 2004 and 2005.

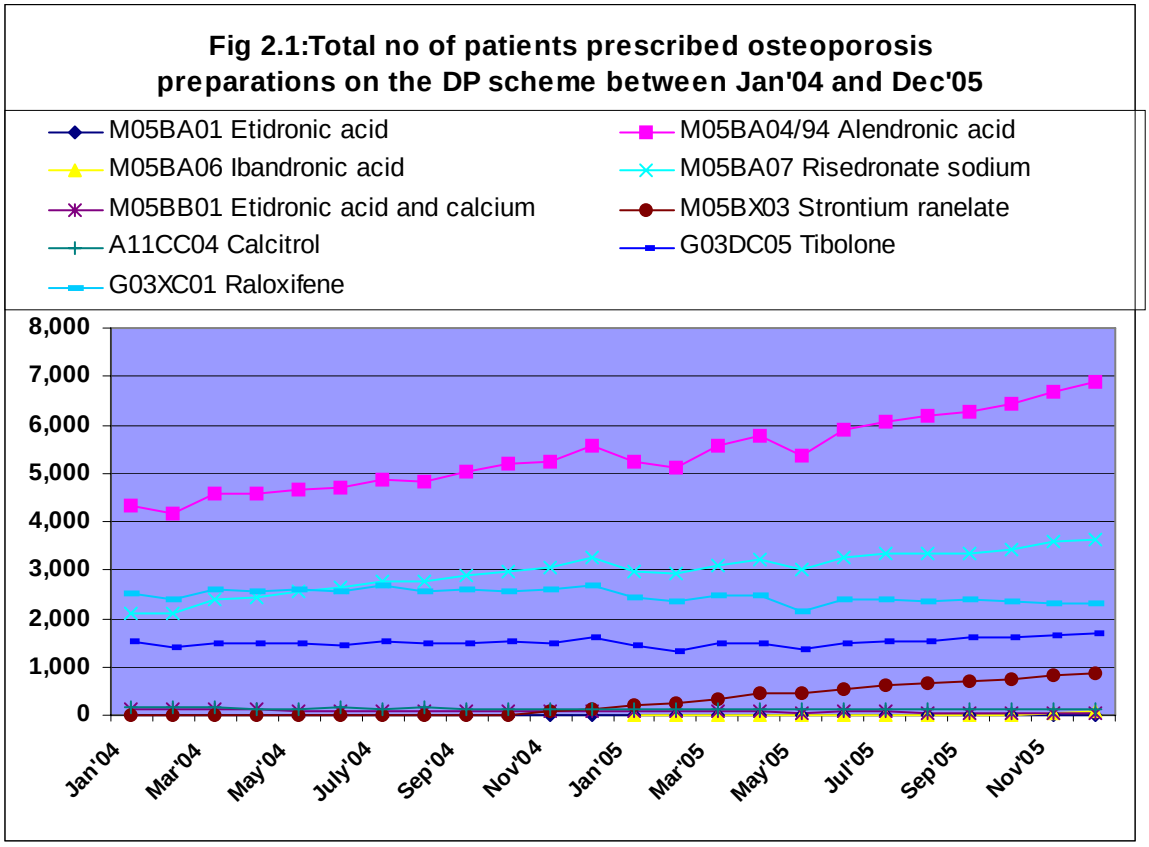
ATC	2,004		2,005	
	Prescs	% of total	Prescs	% of total
M05BB01 Didronel PMO	4,800	1%	3,557	1%
M05BA01 Didronel	1,051	0%	841	0%
M05BA04 Fosamax once weekly	200,739	54%	256,293	55%
M05BA04 Fosamax	3,742	1%	2,882	1%
M05BA94 Fosavance		0%	1,337	0%
M05BA06 Bonviva		0%	274	0%
M05BA07 Actonel	17,093	5%	11,695	3%
M05BA07 Actonel once weekly	81,274	22%	115,187	25%
M05BB07 Actonel combi		0%	736	0%
M05BX03 Protelos grans	285	0%	9,520	2%
G03DC05 Livial	20,062	5%	20,392	4%
G03XC01 Evista	41,399	11%	39,990	9%
	370,445	**100%**	**462,704**	**100%**

Fig 1.6: Total ingredient cost of osteoporosis preparations on the GMS between Jan'04 and Dec'05 (Breakdown by product name)



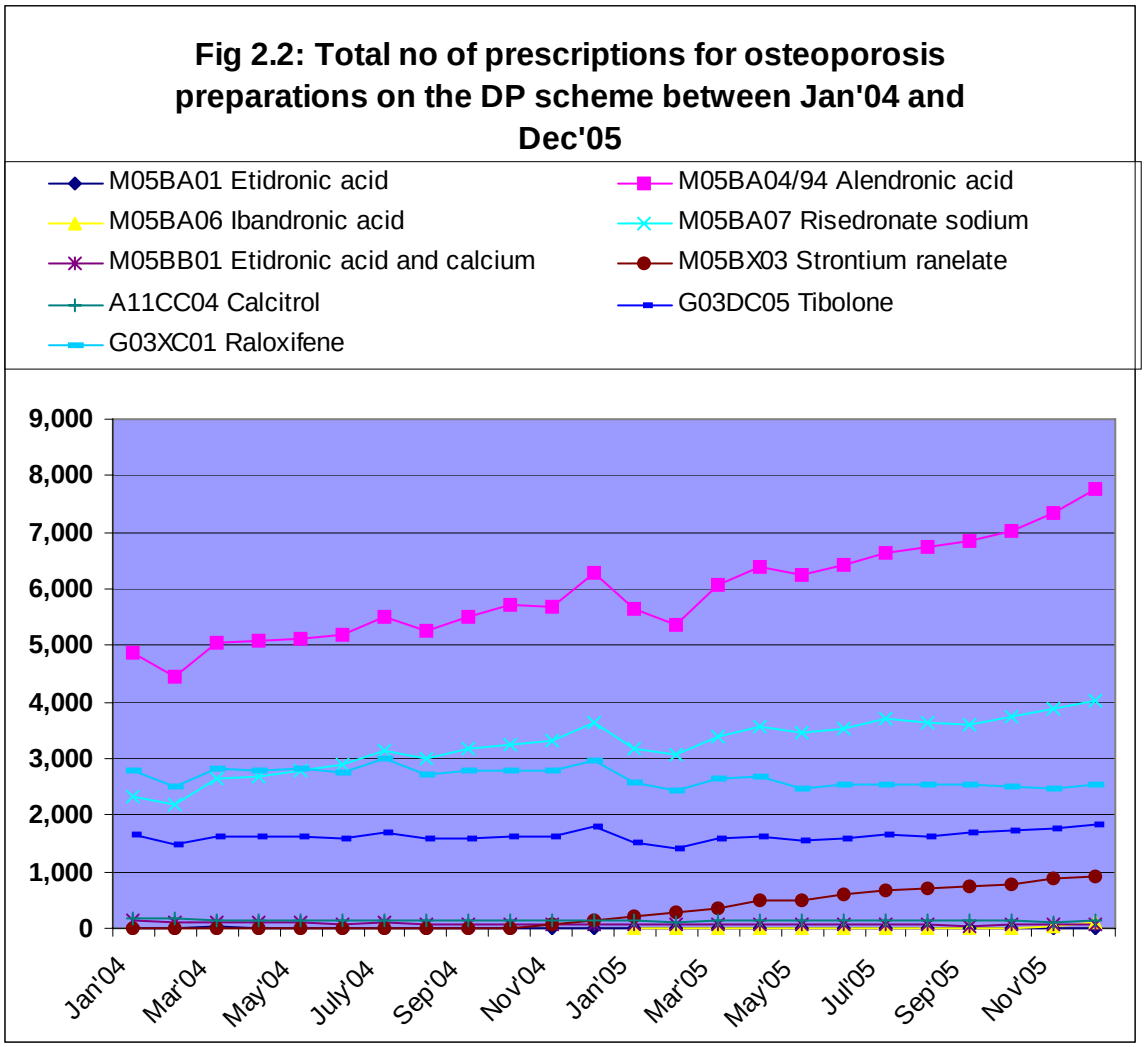
Total ingredient cost of osteoporosis preparations on the GMS for the years ended 2004 and 2005.

	2,004		2,005	
ATC	**Ing Cost**	**% of total**	**Ing Cost**	**% of total**
M05BB01 Didronel PMO	310,211	2%	230,018	1%
M05BA01 Didronel	39,851	0%	31,916	0%
M05BA04 Fosamax once weekly	7,054,320	56%	9,007,142	56%
M05BA04 Fosamax	120,508	1%	91,447	1%
M05BA94 Fosavance		0%	45,759	0%
M05BA06 Bonviva		0%	8,905	0%
M05BA07 Actonel	575,006	5%	392,352	2%
M05BA07 Actonel once weekly	2,947,605	23%	4,177,805	26%
M05BB07 Actonel combi		0%	29,677	0%
M05BX03 Protelos grans	13,032	0%	436,715	3%
G03DC05 Livial	351,500	3%	358,691	2%
G03XC01 Evista	1,250,502	10%	1,210,904	8%
	12,662,534	**100%**	**16,021,331**	**100%**



Total no of patients prescribed osteoporosis preparations on the DP scheme in 2004 and 2005

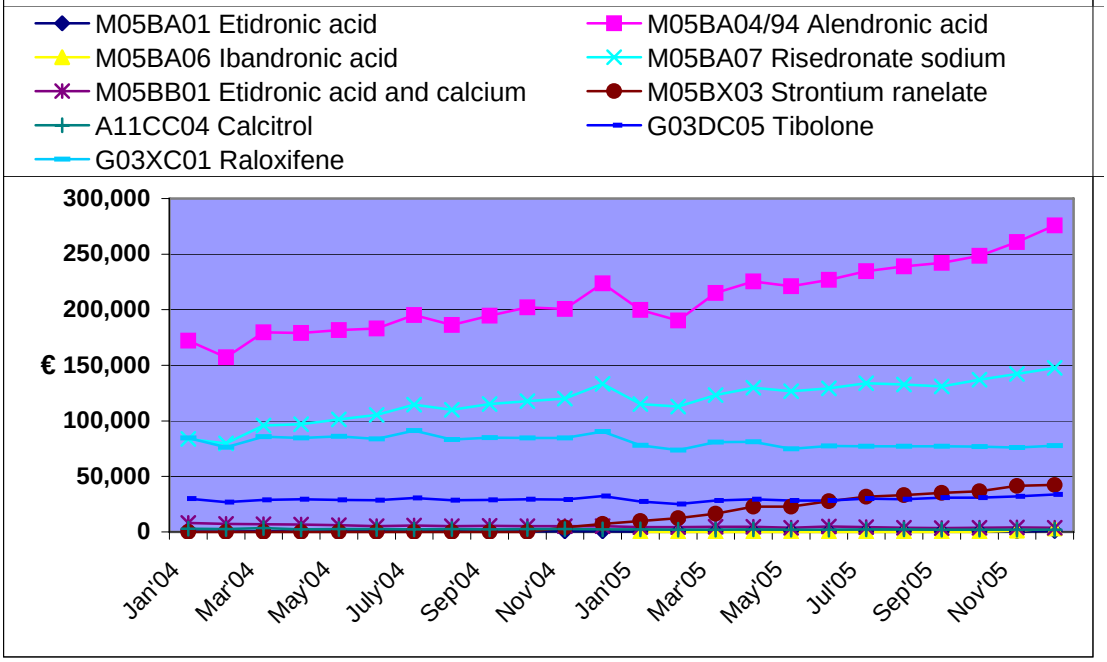
	2004		2005	
	Patients	% of patients	Patients	% of patients
A11CC04 Calcitrol	278	1%	229	1%
G03DC05 Tibolone	3,248	14%	3,253	12%
G03XC01 Raloxifene	4,617	20%	4,087	15%
M05BA01 Etidronic acid	53	0%	34	0%
M05BA04/94 Alendronic acid	9,255	40%	11,348	42%
M05BA06 Ibandronic acid		0%	105	0%
M05BA07 Risedronate sodium	5,332	23%	6,160	23%
M05BB01 Etidronic acid and calcium	467	2%	306	1%
M05BX03 Strontium ranelate	176	1%	1,625	6%
	23,426	**100%**	**27,147**	**100%**



Total no of prescriptions for osteoporosis preparations on the DP scheme in 2004 and 2005

	2004		2005	
	Prescs	% of prescs	Prescs	% of prescs
A11CC04 Calcitrol	1,798	1%	1,563	1%
G03DC05 Tibolone	19,500	13%	19,633	11%
G03XC01 Raloxifene	33,541	22%	30,470	17%
M05BA01 Etidronic acid	158	0%	114	0%
M05BA04/94 Alendronic acid	63,674	41%	78,221	43%
M05BA06 Ibandronic acid		0%	129	0%
M05BA07 Risedronate sodium	35,027	23%	42,842	24%
M05BB01 Etidronic acid and calcium	1,105	1%	761	0%
M05BX03 Strontium ranelate	238	0%	7,120	4%
	155,041	**100%**	**180,853**	**100%**

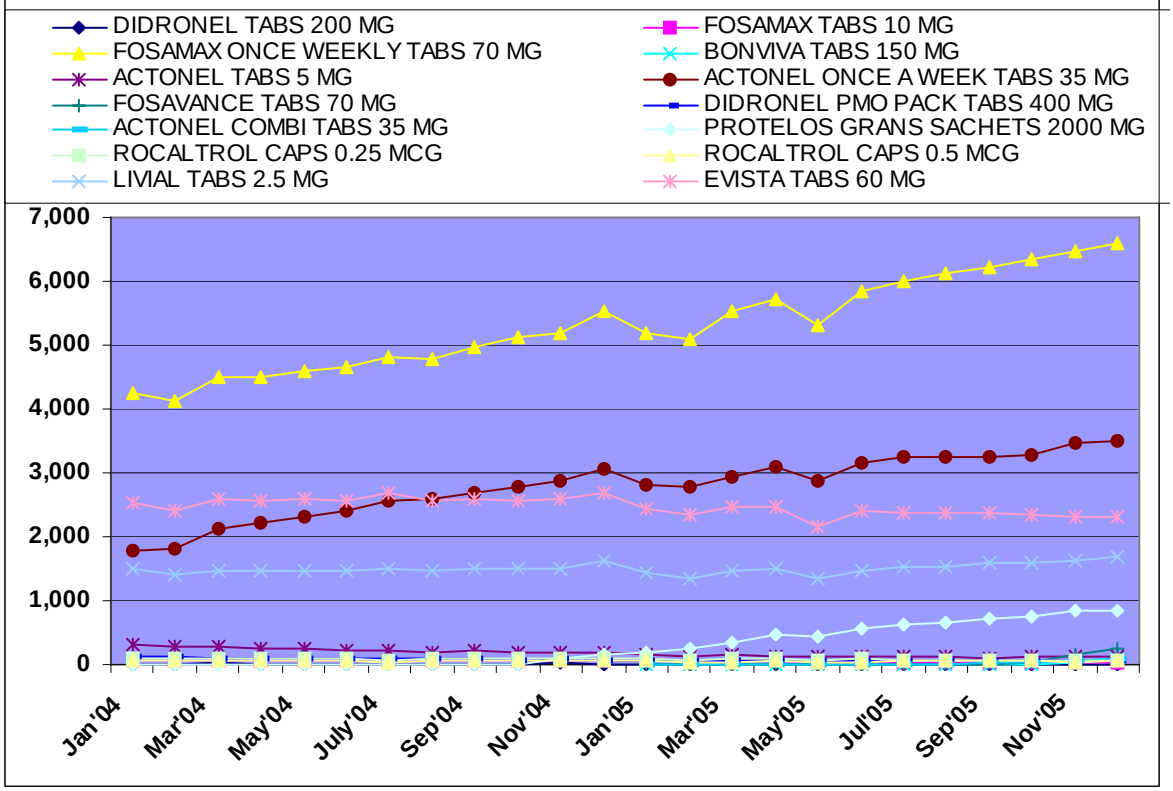
Fig 2.3:Total Ingredient Cost of osteoporosis preparations on the DP scheme between Jan'04 and Dec'05



Total ingredient cost of osteoporosis preparations on the DP scheme in 2004 and 2005

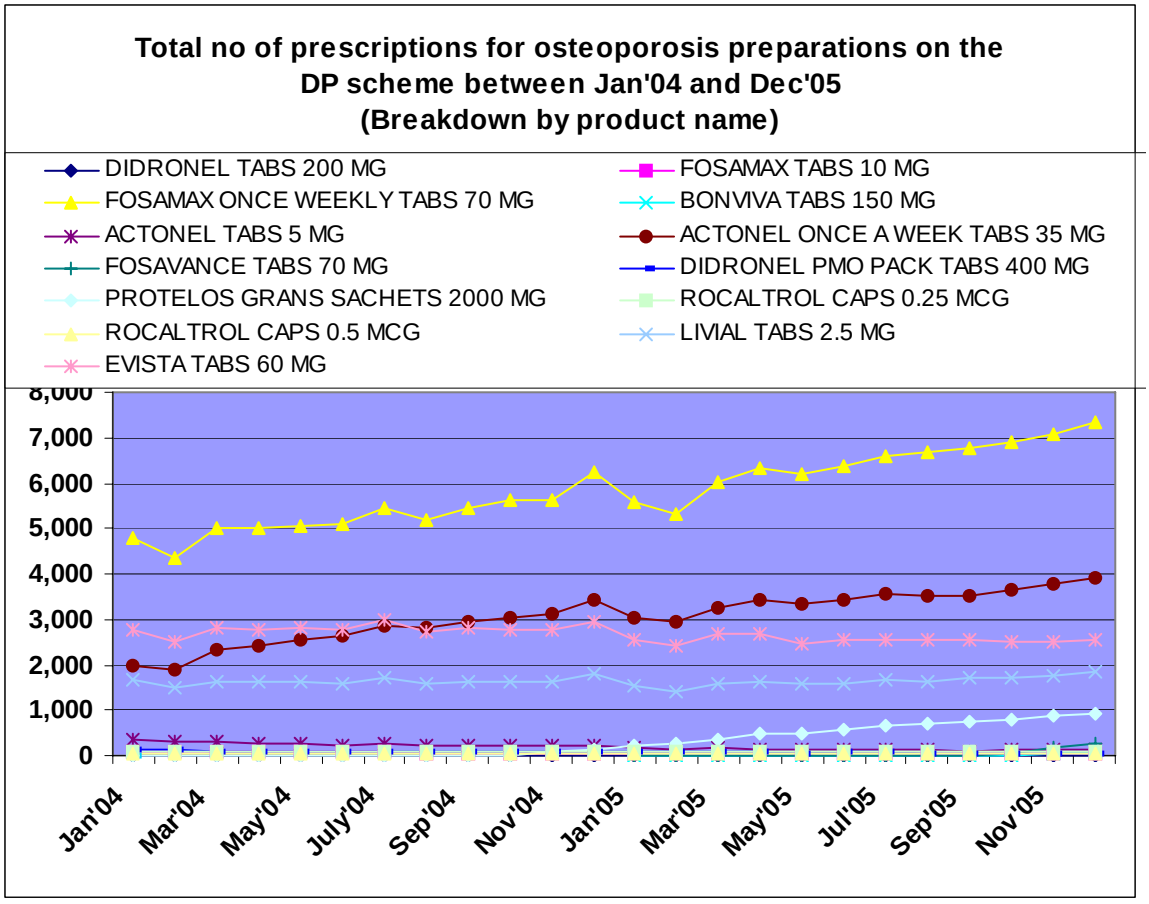
	2004		2005	
	Ing Cost	% of ing cost	Ing Cost	% of ing cost
A11CC04 Calcitrol	31,161	1%	25,948	0%
G03DC05 Tibolone	350,314	7%	353,448	6%
G03XC01 Raloxifene	1,020,371	20%	928,402	15%
M05BA01 Etidronic acid	5,642	0%	4,372	0%
M05BA04/94 Alendronic acid	2,255,463	45%	2,769,271	46%
M05BA06 Ibandronic acid		0%	4,306	0%
M05BA07 Risedronate sodium	1,274,024	25%	1,561,775	26%
M05BB01 Etidronic acid and calcium	71,545	1%	49,313	1%
M05BX03 Strontium ranelate	11,160	0%	332,090	6%
	5,019,680	**100%**	**6,028,925**	**100%**

Fig 2.4: Total no of patients prescribed osteoporosis preparations on the DP scheme between Jan'04 and Dec'05 (Breakdown by product name)



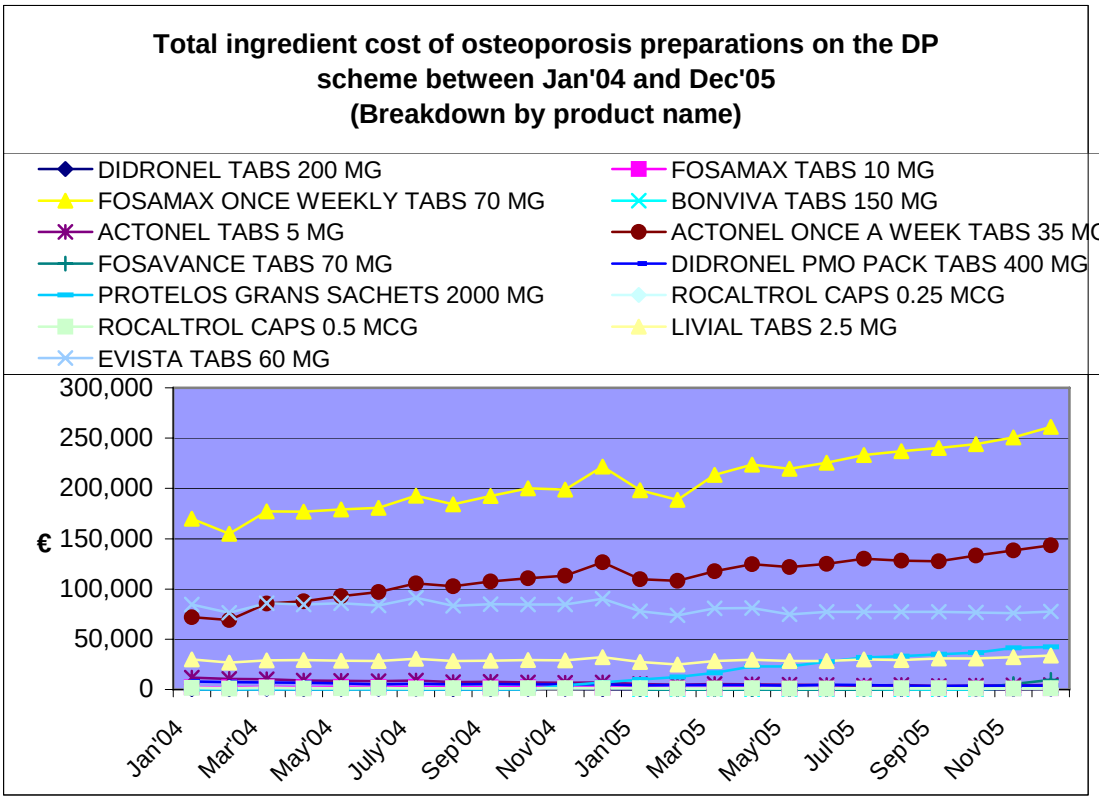
Total no of patients prescribed osteoporosis preparations on the DP scheme in 2004 and 2005

ATC	2004		2005	
	Patients	% of total	Patients	% of total
ACTONEL	546	2%	281	1%
ACTONEL COMBI		0%	120	0%
ACTONEL ONCE A WEEK	4,983	21%	5,955	22%
BONVIVA		0%	105	0%
DIDRONEL	53	0%	34	0%
DIDRONEL PMO PACK	467	2%	306	1%
EVISTA	4,617	19%	4,087	15%
FOSAMAX	159	1%	119	0%
FOSAMAX ONCE WEEKLY	9,156	39%	10,987	40%
FOSAVANCE		0%	291	1%
LIVIAL	3,248	14%	3,241	12%
LIVIAL (P.C.O. MFG.)		0%	50	0%
PROTELOS GRANS	176	1%	1,625	6%
ROCALTROL	278	1%	229	1%
	23,683	**100%**	**27,430**	**100%**



Total no of prescriptions for osteoporosis preparations on the DP scheme in 2004 and 2005

ATC	2004		2005	
	Prescs	% of total	Prescs	% of total
ACTONEL	2,986	2%	1,589	1%
ACTONEL COMBI		0%	250	0%
ACTONEL ONCE A WEEK	32,041	21%	41,253	23%
BONVIVA		0%	129	0%
DIDRONEL	158	0%	114	0%
DIDRONEL PMO PACK	1,105	1%	761	0%
EVISTA	33,541	22%	30,470	17%
FOSAMAX	804	1%	556	0%
FOSAMAX ONCE WEEKLY	62,870	41%	77,190	43%
FOSAVANCE		0%	475	0%
LIVIAL	19,500	13%	19,489	11%
LIVIAL (P.C.O. MFG.)		0%	144	0%
PROTELOS GRANS	238	0%	7,120	4%
ROCALTROL	1,798	1%	1,563	1%
	155,041	**100%**	**181,103**	**100%**



Total ingredient cost of osteoporosis preparations on the DP scheme in 2004 and 2005

ATC	2004		2005	
	Ing Cost	% of total	Ing Cost	% of total
ACTONEL	103,096	2%	53,978	1%
ACTONEL COMBI		0%	10,223	0%
ACTONEL ONCE A WEEK	1,170,928	23%	1,507,797	25%
BONVIVA		0%	4,306	0%
DIDRONEL	5,642	0%	4,372	0%
DIDRONEL PMO PACK	71,545	1%	49,313	1%
EVISTA	1,020,371	20%	928,402	15%
FOSAMAX	26,865	1%	17,652	0%
FOSAMAX ONCE WEEKLY	2,228,598	44%	2,735,165	45%
FOSAVANCE		0%	16,454	0%
LIVIAL	350,314	7%	350,711	6%
LIVIAL (P.C.O. MFG.)		0%	2,737	0%
PROTELOS GRANS	11,160	0%	332,090	5%
ROCALTROL	31,161	1%	25,948	0%
	5,019,680	**100%**	**6,039,148**	**100%**

Number of all patients prescribed drugs affecting bone structure and mineralisation (ATC: M05B) on the GMS scheme in 2005 broken down by individual age groups.

Age Grp	**M05BA01 Etidronic acid**	**M05BA04 Alendronic acid**	**M05BA06 Ibandronic acid**	**M05BA07 Risedronic acid**	**M05BA94 Alendronic acid**	**M05BB01 Etidronic acid +Ca**	**M05BB07 Risedronate Sodium**	**M05BX03 Strontium Ranelate**	**Total**	**% of Total**
0 – 15 yrs	2	16	0	7	2	2	0	1	30	0%
16 – 24 yrs	2	195	0	104	2	7	0	6	316	0.59%
25 – 34 yrs	1	306	1	132	5	7	1	23	476	0.88%
35 – 44 yrs	4	453	3	236	7	14	5	31	753	1.39%
45 – 54 yrs	0	1,391	16	710	31	31	16	106	2,310	4.25%
55- 64 yrs	11	3,928	29	2,147	111	120	55	313	6,714	12.34%
65 – 69 yrs	12	3,648	24	1,888	99	117	32	262	6,082	11.18%
70 – 74 yrs	38	7,460	36	3,633	170	258	80	549	12,224	22.47%
75 yrs +	105	16,025	88	7,229	353	538	132	1,048	25,518	46.88%
	184	**33,422**	**197**	**16,086**	**780**	**1,094**	**321**	**2,339**	**54,423**	

Analysis of all patients prescribed drugs affecting bone structure and mineralisation (ATC: M05B) on the GMS scheme in 2005 broken down by gender.

	Female	% of total	Male	% of total
M05BA01 Etidronic acid	154	0%	30	0%
M05BA04/94 Alendronic acid	29,330	62%	4872	66%
M05BA06 Ibandronic acid	184	0%	13	0%
M05BA07 Risedronate sodium	14,270	30%	2137	29%
M05BB01 Etidronic acid and calcium	972	2%	122	2%
M05BX03 Strontium Ranelate	2,133	5%	206	3%
Total	**47,043**		**7,380**	

Analysis of all patients prescribed drugs affecting bone structure and mineralisation (ATC: M05B) on the DP scheme in 2005 broken down by individual age groups.

Age Grp	M05BA01 Etidronic Acid	M05BA04 Alendronic Acid	M05BA06 Ibandronic Acid	M05BA07 Risedronic Acid	M05BA94 Alendronic Acid	M05BB01 Etidronic acid + Ca	M05BB07 Risedronate Sodium	M05BX03 Strontium Ranelate	Total	
0 - 15 yrs	1	35	0	18	2	0	0	4	60	**0%**
16 - 24 yrs	0	165	0	91	2	8	2	30	298	**1%**
25 - 34 yrs	1	231	1	103	2	6	1	17	362	**2%**
35 - 44 yrs	4	443	5	201	10	11	2	60	736	**3%**
45 - 54 yrs	7	2,204	20	1,300	66	56	33	395	4,081	**19%**
55 - 64 yrs	8	5,603	54	3,288	133	153	64	810	10,113	**48%**
65 - 69 yrs	13	2,904	22	1,400	74	85	19	330	4,847	**23%**
7 - 74 yrs	2	385	3	162	3	8	0	29	592	**3%**
75 yrs +	0	64	1	49	1	3	0	5	146	**1%**
	36	**12,034**	**106**	**6,612**	**293**	**330**	**121**	**1,680**	**21,235**	

Analysis of all prescriptions for drugs affecting bone structure and mineralisation (ATC: M05B) on the DP scheme in 2005 broken down by gender.

	Female	% of total	Male	% of total
M05BA01 Etidronic acid	27	0%	8	0%
M05BA04/94 Alendronic acid	9,876	57%	1,692	61%
M05BA06 Ibandronic acid	93	1%	13	0%
M05BA07 Risedronate sodium	5,415	31%	854	31%
M05BB01 Etidronic acid and Ca	255	1%	53	2%
M05BB07 Risedronate Sodium	113	1%	8	0%
M05BX03 Strontium Ranelate	1,481	9%	160	6%
	17,260		**2,788**	

Approximately 80% of all patients who are dispensed drugs for the management of osteoporosis are prescribed either Fosamax once weekly or Actonel once weekly.

Studies have demonstrated that patients prescribed alendronate 70mg OW and alendronate 10mg daily had equivalent increases in BMD and similar reductions in urine N-telopeptides of type 1 collagen (NTx) corrected for creatinine (Cr) level and bone-specific alkaline phosphatase (BSAP) over 24 months of treatment [13, 14]

Drugs are categorised into 4 classes: 1 – generic, 2 – branded generic, 3 – proprietary drug with a branded or generic equivalent, 4 – proprietary drug with no branded or generic equivalent. All prescription items related to drugs prescribed for the management of osteoporosis were analysed to identify the class of drug prescribed. The result of the analyses identified that all prescriptions for these drugs were related to class 4 i.e. proprietary drugs with no branded or generic equivalent.

Patterns of switching from one drug to another within the group of drugs categorised under (ATC M05) = Drugs for the treatment of bone disease.

Using data from GMS in 2004 and 2005, the following patterns of switching between the various drugs were identified. The drugs listed in the rows indicate the therapy that was initiated and in the columns contain the drugs that they switched to.

Changed to:

Initiated (total)	**Alendronic acid**	**Risedronic acid**	**Strontium Ranelate**	**Other bone therapies**	**Any combinations**
Aledronic acid (n=3311)	**X**	1158 **(34.9%)**	1397 **(42.2%)**	566 **(17.1%)**	190 **(5.7%)**
Risedronic acid (n=1,342)	853 **(59.4%)**	**X**	188 **(13.1%)**	301 **(21%)**	93 **(6.5%)**
Strontium Ranelate (n=128)	78 **(60.9%)**	32 **(25%)**	**X**	11 **(8.6%)**	7 **(5.5%)**

2. Concomitant prescribing of calcium/Vitamin D as an adjunct in the treatment of osteoporosis

Data from 2004/2005 was taken, and concomitant prescribing in the same month was considered.

Patients on any of the M05B drugs were identified and then examined for concomitant prescribing of calcium/Vitamin D.

	Number on bisphosphonates	**N % on concomitant calcium/Vit D**
Total months 2004/2005	54,698	38,717 (70.78%)

By type of osteoporosis drug and whether patients were prescribed concomitant calcium/Vit D in 2004

	Any calcium/Vit D	**Total**
Alendronic acid	18,880 (70.5%)	26,769
Risedronic acid	8,221 (69.9%)	11,759
Other bisphosp/bone drugs	67 (46.1%)	145
Total	27,168 (70.2%)	38,673

By type of osteoporosis and whether patients were prescribed concomitant calcium/Vit D in 2005

	Any calcium/Vit D	**Total**
Alendronic acid	23,993 (74.0%)	32,446
Risedronic acid	10,295 (72.5%)	14,199
Other bisphosp	223 (39.9%)	559
Total	34,511	47,204

3. Analysis of prescribing of prednisolone of doses >7.5mg per day for a duration exceeding 3 months. Co-prescribing of recognised treatments for osteoporosis considered.

Analysing GMS data for 2004 and 2005, the following is the number of months that patients were prescribed >7.5mg of prednisolone per day.

2004 - number of months received	**Number of patients with >7.5mg/day prednisolone**	**%**
1	23,374	57.07%
2	7,074	17.27%
3	3,471	8.47%
4	1,979	4.83%
5	1,263	3.08%
6	868	2.12%
7	639	1.56%
8	586	1.43%
9	468	1.14%
10	458	1.12%
11	421	1.03%
12	358	0.87%
Total	40,959	

2005 - number of months received	Number of patients with >7.5mg/day prednisolone	%
1	24,254	58.34%
2	7,024	16.90%
3	3,358	8.08%
4	1,920	4.62%
5	1,225	2.95%
6	914	2.20%
7	656	1.58%
8	524	1.26%
9	515	1.24%
10	451	1.08%
11	405	0.97%
12	324	0.78%
Total	**41,570**	

Only those patients who received 4+ months prescriptions per year in either 2004 or 2005, were included in the study.(N= **9,525**)

A small proportion of these received bisphosphonates or other treatments for osteoporosis prior to receiving prednisolone **(808, 8.5%)** and were excluded from further analysis.

The table below shows the subsequent use of bisphosphonates or other therapies for bone disease (all M05B) by duration of prednisolone (over 2004 and 2005). There was a statistically significant difference between use of any osteoporosis medication and duration of prednisolone (dose response, chi-square test, $p<0.0001$).

(N=8,717) Duration of treatment of prednisolone and subsequent use of bisphosphonates

	4-5 months	6-8 months	9-12 months	12-14 months	15+ months
No osteoporosis drugs	1,810 **(73.4%)**	1,611 **(66.1%)**	753 **(57.3%)**	433 **(50.6%)**	701 **(42.7%)**
Any osteoporosis drugs	655 **(26.6%)**	828 **(33.9%)**	562 **(42.7%)**	422 **(49.4%)**	942 **(57.3%)**
Total	**2,465**	**2,439**	**1,315**	**855**	**1,643**

The following table is by type of osteoporosis therapy started.

	4-5 months	**6-8 months**	**9-12 months**	**12-14 months**	**15+ months**
No osteoporosis drugs	1,810 **(73.4%)**	1,611 **(66.1%)**	753 **(57.3%)**	433 **(50.6%)**	701 **(42.7%)**
Alendronic acid	451 **(18.3%)**	559 **(22.9%)**	376 **(28.59%)**	289 **(33.8%)**	642 **(39.1%)**
Risedronic acid	188 **(7.62%)**	254 **(10.4%)**	176 **(13.38%)**	123 **(14.4%)**	289 **(17.6%)**
Strontium Ranelate	7 **(.28%)**	12 **(.49%)**	4 **(.30%)**	4 **(.47%)**	8 **(0.49%)**
Other osteoporosis drugs	9 **(.36%)**	3 **(.12%)**	6 **(.45%)**	6 **(0.7%)**	3 **(0.18%)**
Total	**2,465**	**2,439**	**1,315**	**855**	**1,643**

4. Potential drug interactions involving medications for the prophylaxis and treatment of osteoporosis.

Drug Interactions

A drug interaction may occur if the effect of a drug is altered by the presence of another drug, food, drink or environmental agent. The main risk factors for clinically significant drug interactions include drugs with a narrow therapeutic index, patient age and genetic characteristics. Some of the information sources on drug interactions include the British National Formulary (BNF), Stockley's Drug Interactions and the National Medicines Information Centre (NMIC).

Risk factors for drug interactions

1. **Drugs with a narrow therapeutic index** i.e. where there is a small margin between therapeutic and toxic drug levels e.g. digoxin, lithium, phenytoin, theophylline, warfarin and tricyclic antidepressants
2. **High risk patients** such as the a) the elderly due to polypharmacy, b) patients with renal or hepatic impairment either age-related or otherwise may alter drug disposition
3. **Genetic characteristics** may result in significant pharmacokinetic differences e.g. approximately 8% of the population will be poor metabolisers of drugs metabolised by cytochrome P450 2D6.

Methodology

As per British National Formulary (BNF**) March 2006 edition and Stockley's Drug Interactions** seventh edition all drugs were identified that could potentially interact with each drug prescribed for the management of osteoporosis on the GMS. Using SAS statistical software all prescriptions for drugs affecting bone metabolism were selected for all healthboard regions between January 2005 and December 2005. All prescriptions on the GMS between Jan'2005 and Dec'2005 were then analysed to identify the frequency of co-prescribing of potentially interactive drugs.

Each class of drugs were analysed separately ie Bisphosphonates and all drugs which come under this drug group (ATC M05BA, M05BB), Strontium Ranelate (ATC M05BX03), Raloxifene (ATC G03XC01), Tibolone (ATC G03DC05)

Included in the analysis were all items on the same prescription claim over the 12 month period January 2005 to December 2005.

The following tables give the total number of co-prescribed potentially interacting drug prescriptions and total osteoporosis drug prescriptions.

1. **Bisphosphonates**

Maalox, antacids, calcium-rich foods, calcium supplements, iron preparations, magnesium-containing laxatives or milk.

The oral absorption of bisphosphonates is reduced by Maalox and by other antacids, calcium-rich foods, calcium supplements, iron preparations, magnesium-containing laxatives or milk. Administration should be separated to avoid a reduction in absorption i.e. patients should wait at least 30 mins after taking alendronate before taking any other food or drug.

2. **Bisphosphonates;**

Clodronate (M05BA02) and Aminoglycosides (J01G)

There were no prescriptions for clondronate

Patient manifested with severe hypocalcaemia after a course of netilmicin (J01GB07) and amikacin (J01GB06). It appears that the addition of an aminoglycoside can

precipitate severe hypocalcaemia. Close monitoring of calcium and magnesium levels is required on patients taking an aminoglycoside with a bisphosphonate.

		Adverse Drug Reaction
	N (%)	**Quinolones (J01M) and Tetracyclines (J01A).** The maker predicts that strontium will complex with quinolones and tetracyclines, so preventing their absorption. Because of this, they recommend that when treatment with quinolones or tetracyclines is required, strontium ranelate therapy should be temporarily suspended.
Strontium with Quinolones	27 (0.32%)	
Total Strontium scripts	8,354	
	N (%)	
Strontium with Tetracyclines	21 (0.25%)	
Total Strontium scripts	8,354	
	N (%)	Because of the increased fibrinolytic activity identified in patients who were co-prescribed tibolone with anticoagulants. It is advised that until more is known about the exact effects patient on tibolone with anticoagulant therapy should be closely monitored.
Tibolone with anticoagulant therapy	2,391 (13.2%)	
Total Tibolone scripts	18,146	
	N (%)	Tibolone may slightly impair glucose tolerance and therefore potentially reduce the effects of hypoglycaemics. Patients with diabetes who are prescribed tibolone need to be closely monitored,
Tibolone with anti-glycaemic drugs	407 (2.2%)	
Total Tibolone scripts	18,146	
	N (%)	The effects of tibolone may be reduced by enzyme-inducing anticonvulsants and rifampicin Barbiturates **N05CA, N05CB** Phenytoin **N03AB02, N03AB52** Carbamazepine **N03AF01**
Tibolone with EID	393 (2.17%)	
Total Tibolone scripts	18,146	

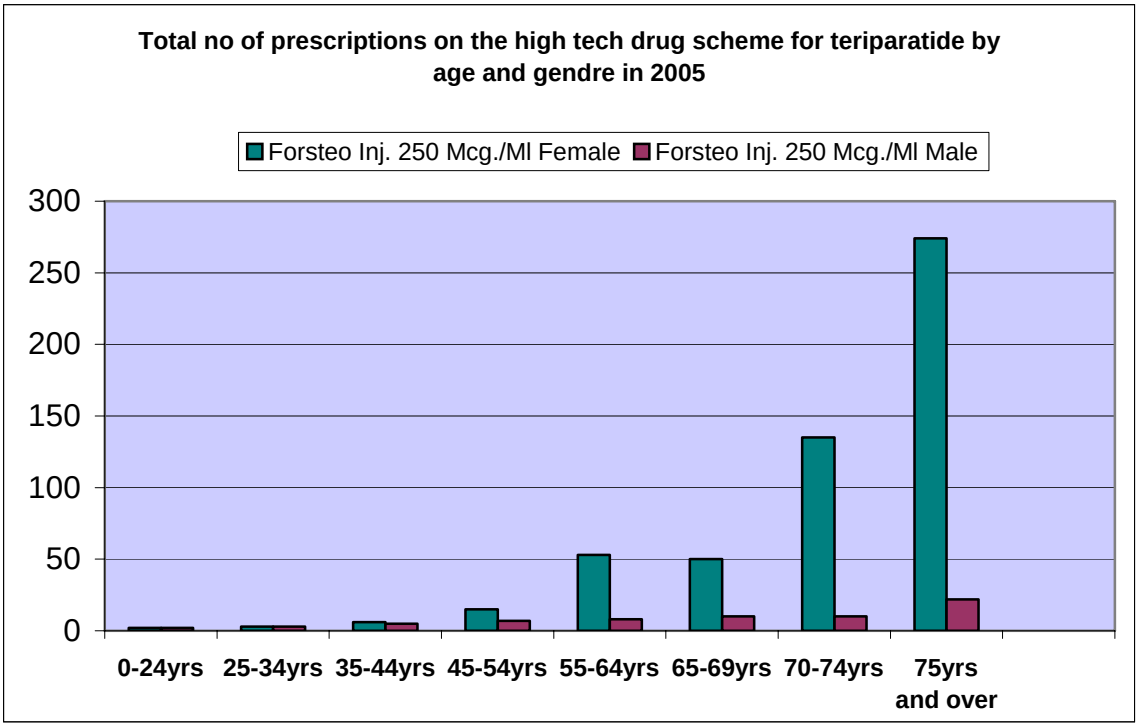
EID=Enzyme inducing drugs
There were no scripts for Rifampicin

	N (%)	**Raloxifene and colestyramine (ATC code C10AC01)** The makers report that the concurrent use of colestyramine twice daily reduced the absorption of raloxifene by about 40% due to an interruption in enterohepatic cycling. It is recommended that these two drugs should not be used concurrently.
Colestyramine with raloxifene	42 (0.11%)	
Raloxifene scripts	**38,941**	

Co-prescribing with PPIs

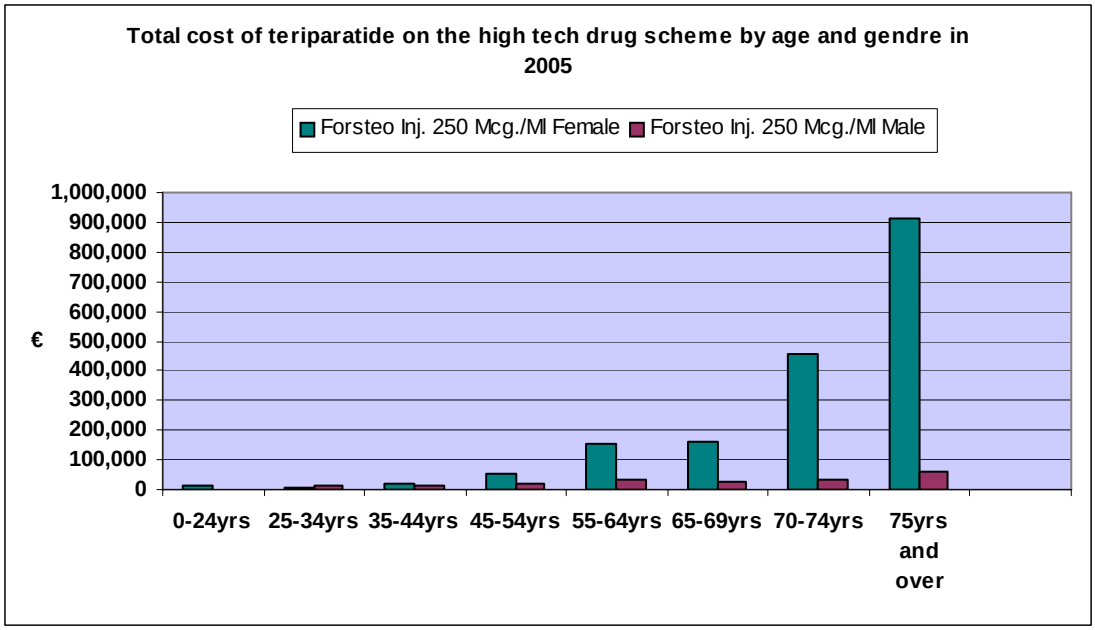
	N (%)
PPIs with any drug used in the treatment of bone disease (ATC :M05B) 87,083 **(22.0%)** All scripts for osteoporosis drugs 395,738	
	N (%)
PPIs with bisphosphonate (ATC: M05BA) 84,584 **(22.1%)** All scripts for bisphosphonates 382,356	
	N (%)
PPIs with other bisphosp (ATC : M05BB) with calcium 608 **(14.4%)** All scripts for other bisphosphonates 4,229	
	N (%)
PPIs with other drugs used in the treatment of bone disease (M05BX) 1,927 **(20.7%)** All scripts for other drugs used in the treatment of bone disease 9,319	

5. Prescribing of teriparatide on the High Tech Drugs scheme



Total no of prescriptions for teriparatide on the High Tech Drug Scheme by age and gender in 2005

	Forsteo Inj. 250 Mcg./Ml		Forsteo Inj. 250 Mcg./Ml			
	Female	%	Male	%	Total	% of total
0-24yrs	2	0%	2	3%	4	1%
25-34yrs	3	1%	3	4%	6	1%
35-44yrs	6	1%	5	7%	11	2%
45-54yrs	15	3%	7	10%	22	4%
55-64yrs	53	10%	8	12%	61	10%
65-69yrs	50	9%	10	15%	60	10%
70-74yrs	135	25%	10	15%	145	24%
75yrs and over	274	51%	22	33%	297	49%
	538	100%	67	100%	606	100%

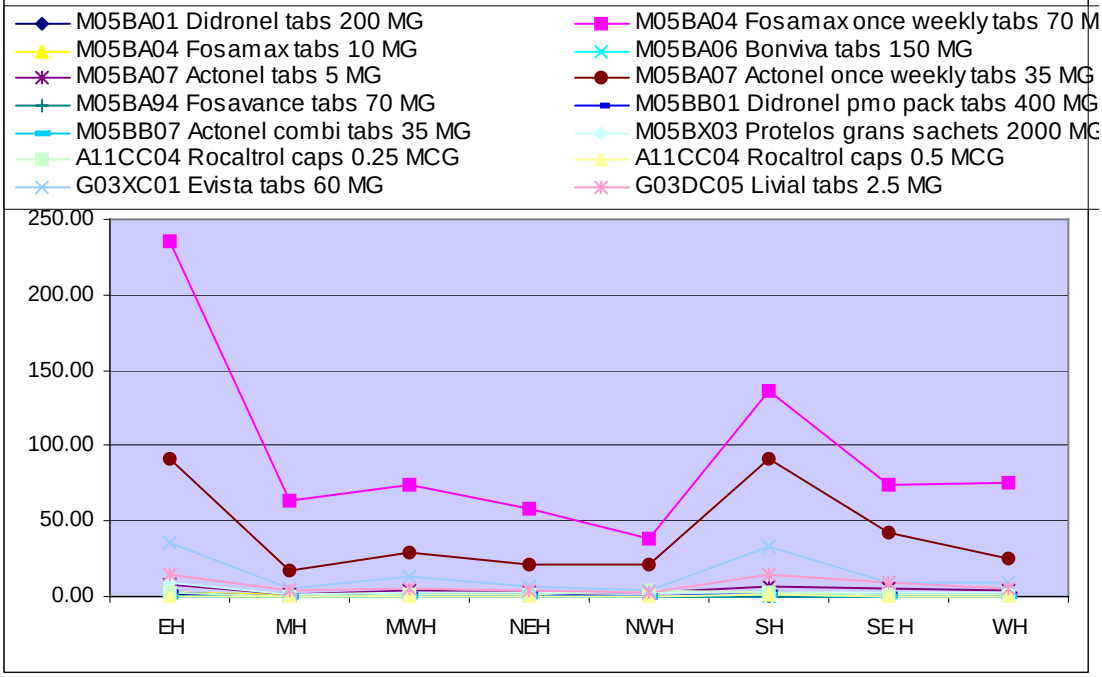


Total ingredient cost (€) of teriparatide on the High Tech Drug Scheme by age and gender in 2005

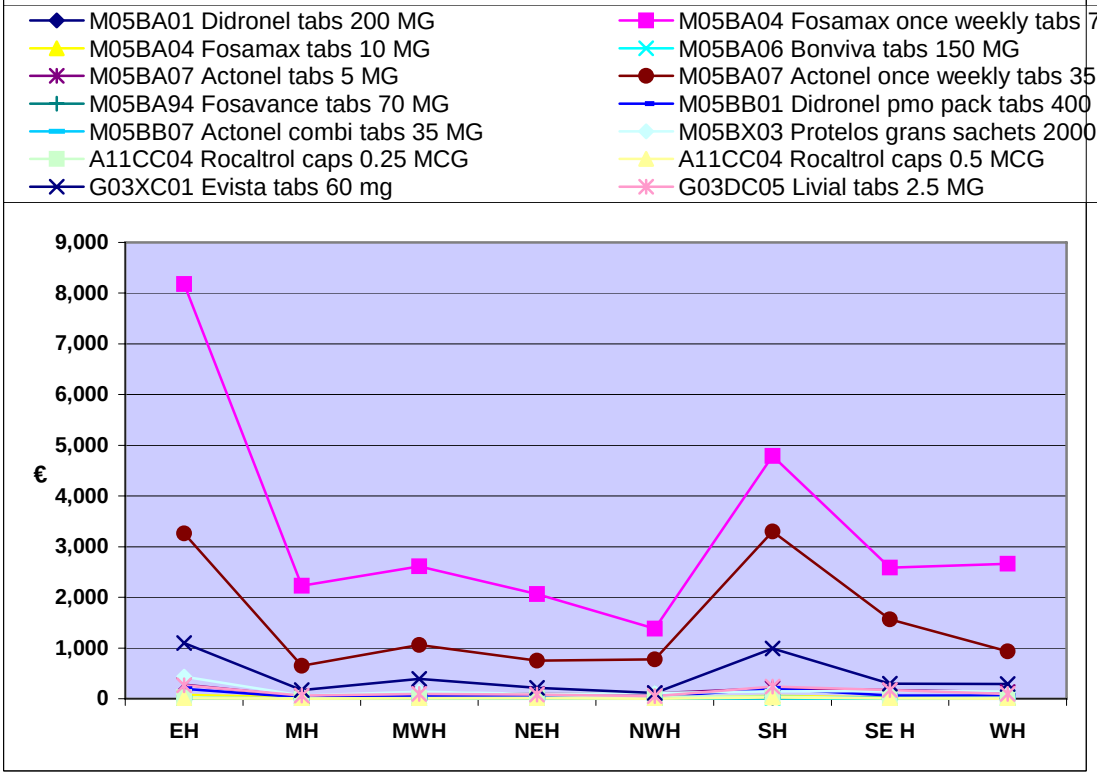
	Forsteo Inj. 250 Mcg./Ml		Forsteo Inj. 250 Mcg./Ml			
	Female	%	Male	%	Total	% of total
0-24yrs	10,455	1%	909	0%	11,365	1%
25-34yrs	5,455	0%	10,910	5%	16,365	1%
35-44yrs	21,365	1%	12,728	6%	34,094	2%
45-54yrs	56,823	3%	19,092	10%	75,915	4%
55-64yrs	156,830	9%	35,457	18%	192,287	10%
65-69yrs	164,103	9%	28,639	14%	192,742	10%
70-74yrs	455,489	26%	31,366	16%	486,855	25%
75yrs and over	915,524	51%	60,914	30%	976,438	49%
	1,786,045	100%	200,015	100%	1,986,061	100%

6. Regional variations in the prescribing of medicines for prophylaxis and treatment of osteoporosis. Results are standardised per 1000 GMS eligible population for each of the Health Board Regions

Total no of prescriptions dispensed for osteoporosis therapy on the GMS in 2005 in all healthboard regions (results are standardised per 1000 GMS eligible population for each of the healthboard regions)



Total ingredient cost of osteoporosis therapy to the GMS in 2005 (results standardised per 1000 GMS eligible population for each of the healthboard regions



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Appendix 1

Patients				
	2004		**2005**	
ATC	**patients**	**% of total**	**patients**	**% of total**
M05BA01 Etidronic acid	222	0%	173	0%
M05BA04/94 Alendronic acid	27,309	26%	32,615	26%
M05BA06 Ibandronic acid		0%	197	0%
M05BA07 Risedronic acid	14,404	14%	15,568	13%
M05BB01 Etidronic acid and calcium	1,572	2%	1,051	1%
M05BB07 Risedronate Sodium		0%	315	0%
M05BX03 Strontium ranelate	218	0%	2,283	2%
A11CC04 Calcitriol	763	1%	678	1%
A12AX91 Calcium	51,474	50%	63,839	51%
G03DC05 Tibolone	2,968	3%	3,014	2%
G03XC01 Raloxifene	4,941	5%	4,498	4%
	103,871	**100%**	**124,231**	**100%**

Prescs				
	2004		**2005**	
ATC	**Prescs**	**% of total**	**Prescs**	**% of total**
M05BA01 Etidronic acid	1,051	0%	841	0%
M05BA04/94 Alendronic acid	204,481	66%	260,512	65%
M05BA06 Ibandronic acid		0%	274	0%
M05BA07 Risedronic acid	98,367	32%	126,882	32%
M05BB01 Etidronic acid and calcium	4,800	2%	3,557	1%
M05BB07 Risedronate Sodium		0%	736	0%
M05BX03 Strontium ranelate	285	0%	9,520	2%
A11CC04 Calcitriol	6,299		5,709	
A12AX91 Calcium	342,588		444,503	
G03DC05 Tibolone	20,062		20,392	
G03XC01 Raloxifene	41,399		39,990	
	719,332	**100%**	**912,916**	**100%**

Ing Cost				
	2004		**2005**	
ATC	**Ing Cost**	**% of total**	**Ing Cost**	**% of total**
M05BA01 Etidronic acid	39,851	0%	31,916	0%
M05BA04/94 Alendronic acid	7,174,828	46%	9,144,348	46%
M05BA06 Ibandronic acid		0%	8,905	0%
M05BA07 Risedronic acid	3,522,611	23%	4,570,157	23%
M05BB01 Etidronic acid and calcium	310,211	2%	230,018	1%
M05BB07 Risedronate Sodium		0%	29,677	0%
M05BX03 Strontium ranelate	13,032	0%	436,715	2%
A11CC04 Calcitriol	81,161	1%	72,345	0%
A12AX91 Calcium	2,753,481	18%	3,590,910	18%
G03DC05 Tibolone	351,500	2%	358,691	2%
G03XC01 Raloxifene	1,250,502	8%	1,210,904	6%
	15,497,176	**100%**	**19,684,586**	**100%**

Patients

ATC	2,004		2,005	
	patients	% of total	patients	% of total
M05BB01 Didronel PMO	1,492	1%	1,051	1%
M05BA01 Didronel	211	0%	173	0%
M05BA04 Fosamax once weekly	25,130	24%	31,233	24%
M05BA04 Fosamax	674	1%	604	0%
M05BA94 Fosavance		0%	778	1%
M05BA06 Bonviva		0%	197	0%
M05BA07 Actonel	2,349	2%	1,529	1%
M05BA07 Actonel once weekly	11,370	11%	14,039	11%
M05BB07 Actonel combi		0%	315	0%
M05BX03 Protelos grans	218	0%	2,283	2%
A11CC04 Rocaltrol	763	1%	678	1%
A12AX91 Calcichew-D3	631	1%		0%
A12AX91 Calcichew-D3 Forte	35,116	34%	44,218	35%
A12AX91 Ideos(P.C.O. MFG.) chewable	103	0%	504	0%
A12AX91 Ideos chewable	15,227	15%	17,868	14%
A12AX91Osteofos D3	3,173	3%	4,531	4%
G03DC05 Livial	2,968	3%	3,056	2%
G03XC01 Evista	4,941	5%	4,498	4%
	104,366		**127,555**	

Prescriprions

ATC	2,004		2,005	
	Prescs	% of total	Prescs	% of total
M05BB01 Didronel PMO	4,800	1%	3,557	0%
M05BA01 Didronel	1,051	0%	841	0%
M05BA04 Fosamax once weekly	200,739	28%	256,293	28%
M05BA04 Fosamax	3,742	1%	2,882	0%
M05BA94 Fosavance		0%	1,337	0%
M05BA06 Bonviva		0%	274	0%
M05BA07 Actonel	17,093	2%	11,695	1%
M05BA07 Actonel once weekly	81,274	11%	115,187	13%
M05BB07 Actonel combi		0%	736	0%
M05BX03 Protelos grans	285	0%	9,520	1%
A11CC04 Rocaltrol	6,299	1%	5,709	1%
A12AX91 Calcichew-D3	1,387	0%		0%
A12AX91 Calcichew-D3 Forte	230,867	32%	305,076	33%
A12AX91 Ideos(P.C.O. MFG.) chewable	131	0%	1,470	0%
A12AX91 Ideos chewable	96,733	13%	116,700	13%
A12AX91Osteofos D3	13,470	2%	21,257	2%
G03DC05 Livial	20,062	3%	20,392	2%
G03XC01 Evista	41,399	6%	39,990	4%
	719,332		**912,916**	

Ingredient Cost

	2,004		2,005	
ATC	**Ing Cost**	**% of total**	**Ing Cost**	**% of total**
M05BB01 Didronel PMO	310,211	2%	230,018	1%
M05BA01 Didronel	39,851	0%	31,916	0%
M05BA04 Fosamax once weekly	7,054,320	46%	9,007,142	46%
M05BA04 Fosamax	120,508	1%	91,447	0%
M05BA94 Fosavance		0%	45,759	0%
M05BA06 Bonviva		0%	8,905	0%
M05BA07 Actonel	575,006	4%	392,352	2%
M05BA07 Actonel once weekly	2,947,605	19%	4,177,805	21%
M05BB07 Actonel combi		0%	29,677	0%
M05BX03 Protelos grans	13,032	0%	436,715	2%
A11CC04 Rocaltrol	81,161	1%	72,345	0%
A12AX91 Calcichew-D3	11,232	0%		0%
A12AX91 Calcichew-D3 Forte	1,690,196	11%	2,253,081	11%
A12AX91 Ideos(P.C.O. MFG.) chewable	1,133	0%	13,092	0%
A12AX91 Ideos chewable	899,626	6%	1,085,946	6%
A12AX91Osteofos D3	151,295	1%	238,791	1%
G03DC05 Livial	351,500	2%	358,691	2%
G03XC01 Evista	1,250,502	8%	1,210,904	6%
	15,497,176	**100%**	**19,684,585**	**100%**