

Pharmacotherapy costs and medicines reimbursement policies of osteoporosis in the Republic of Bulgaria and Republic of North Macedonia

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Abstract

The aim of the present study was to analyze and compare the number of health insured persons suffering from osteoporosis and antiosteoporotic drugs reimbursed by the National Health Insurance Funds (NHIF) in the Republic of Bulgaria (RBG) and Republic of North Macedonia (RNM) for the period 2015–2018. The reimbursement cost paid by the NHIF for the same period in both countries was surveyed.

The results show an increase in both the number of patients with osteoporosis and the cost of the treatment. The most prescribed drug in R. Bulgaria is *denosumab* and it has the highest costs respectively, while in R.N. Macedonia the most prescribed and respectively the most expensive treatment is the bisphosphonate *ibandronic acid*, tablets of 150 mg. The trend of rising costs in both countries is likely to continue due to the increasing number of patients with osteoporosis.

The number of patients and cost of pharmacotherapy in RNM and RBG are increasing but the reimbursement policy in RNM is more restrictive in terms of reimbursed medicines. On the other side, the RNM is with a higher level of reimbursement that might positively affect the cost of pharmacotherapy.

Keywords

bisphosphonate, Health Insurance Fund, reimbursement status

Introduction

Osteoporosis is a progressive, metabolic disease that affects the skeletal system and is characterized by micro-structural deterioration in bone tissue and a decrease in bone strength (WHO 1994; Sözen et al. 2017). It is also called a “silent epidemic disease” because it usually does not include any symptoms until the disease progresses and often goes unnoticed (NIH 2018). Osteoporosis is a global health concern of the 21st century, which is ex-

pected to increase with the aging population (Sunil and Bhaskar 2012; Barker et al. 2016). It is a long-term condition that affects the quality of life. Affected patients often experience a pain, activity limitations, mood swings, and social isolation (Al Anouti et al. 2019; Chakuleska et al. 2019).

There are no officially published recent data on the epidemiology of osteoporosis in Bulgaria. 426,000 women over the age of 50 (26.6%) have had osteoporosis of the spine or femoral neck (data 2008–2010) (Borisova et al. 2019).

One of the most serious complications is the fracture, which can occur after a minor injury. The risk of fractures increases significantly with age. The most common fractures are of the femur, spine, pelvis, proximal tibia. The consequences of severe fractures result in increased morbidity and mortality (Blackie 2020). In 2010, about 22 million women and 5.5 million men were diagnosed with osteoporosis in the European Union, and those with already realized hip fracture were 3.3 million. In the same year, the number of new fractures was 3.5 million, including 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (of the ribs, pelvis, humerus, etc.). Two-thirds of all new fractures occur in women. The incidence of osteoporotic fractures is expected to increase (future demographic changes) to 4.5 million per year in 2025 (Borisova et al. 2019).

Fractures are associated with the appearance of acute pain, in some cases, depending on the location, to loss of function, and the need of hospitalization. The recovery process is slow and incomplete and can affect patients' mobility and social distance (Shoback et al. 2020). Fractures of the hip, vertebrae, and distal radius are associated with increased mortality (Chakuleska et al. 2018; Eastell et al. 2019). In addition to impairing the quality of life of patients suffering from osteoporosis, the economic burden is also important (Lewiecki et al. 2019; Fogel and Jenis 2020). Fractures in osteoporosis are often associated with the direct use of hospital care, long-term care, and illness (Hernlund et al. 2013; Dunnewind et al. 2017). Timely diagnosis and selection of the right therapy are essential to reduce the risk of fractures.

According to various therapeutic guidelines (Nutri et al. 2017; Kanis et al. 2019), the goal of prevention and treatment of osteoporosis is to prevent the fractures, reduce the incidence of new fractures, and influence risk factors. The prevention and treatment strategy includes pharmacological and non-pharmacological components. The choice of appropriate therapy for each patient is individual and depends on the bone mineral density (BMD), family predisposition, patient's age, the presence of fractures and the risk of falls (Briot et al. 2018).

Prevention and basic therapy include lifestyle changes with physical activity, avoidance of alcohol consumption, smoking cessation, and consumption of healthy food with sufficient intake of calcium and vitamin D. In case of insufficient intake of these elements in the diet, the use of dietary supplements with calcium and vitamin D is recommended. A minimum daily intake of 1000 mg of calcium and 800–1000 IU of vitamin D is recommended for all patients with osteoporosis (Sunyecz 2008).

Pharmacotherapy includes treatment with different pharmacological groups, mainly bisphosphonates (BPs) as first-line drugs (Compston et al. 2017; Borisova et al. 2019). The commonly used BPs are:

- *Alendronate*, tablets 70 mg, administered once a week, half an hour before breakfast with enough water; the patient should remain upright for half an hour after taking the drug;
- *Risedronate*, tablets 35 mg, used once a week in the morning;

- *Ibandronate*, tablets 150 mg, once monthly in the morning or 3 mg by intravenous administration every 3 months;
- *Zoledronic acid*, 5 mg by intravenous injection once a year.

Other drugs used for the prevention and treatment of fractures are:

- *Denosumab*, a fully-humanized monoclonal antibody that binds to RANKL and prevents RANK activation. It is administered subcutaneously in a dose of 60 mg once every 6 months.
- *Strontium ranelate*, 2 g daily, taken orally two hours after meals, preferably at bedtime. The Committee for Pharmaceutical Risk Assessment of the European Medicinal Agency (EMA) in January 2014 recommended that the use of strontium ranelate be discontinued, due to the occurrence of unexpected cardiovascular and thromboembolic complications (EMA/10206/2014).
- *Teriparatide* (recombinant human parathyroid hormone) 20 µg is given once daily by subcutaneous injection for a maximum of 24 months.
- *PTH (parathyroid hormone)* (1–84) 100 µg is administered by subcutaneous injection once daily for a maximum of 24 months.

Hormone replacement therapy, in particular oestrogens, are also used in the prophylaxis and treatment of osteoporosis.

- *Estradiol* 1–2 mg/ day p.o. or a transdermal patch that releases 25–50 µg estradiol per day or 0.5–1.5 mg estradiol gel once daily applied on the skin. Progestin is added depending on the condition of the menopause, especially if the patient has had a hysterectomy.
- *Raloxifene* 60 mg is a selective oestrogen receptor modulator (SERM) and is administered orally once daily.
- *Tibolone* 2.5 mg activates bone oestrogen receptors and is administered orally once daily.

The success of pharmacological therapy is assessed by measuring bone density and at the population level by reducing complications.

Although the osteoporosis is having high economic burden on the reimbursement institutions, little is known about the cost of this disease in Bulgaria and Macedonia (Vasilev et al. 2003a, b; Savova et al. 2012).

The aim of the present study was to analyze and compare the number of health insured persons suffering from osteoporosis and antiosteoporotic drugs reimbursed by the NHIF in RBG and RNM for the period 2015–2018.

Materials and methods

The present study is a retrospective analysis of the number of patients with the respective International Classification

of Diseases (ICDs) codes by years and costs of the NHIF for the pharmacotherapy of the diagnoses summarized in osteoporosis group for the period 2015–2018 in both countries.

The analysis of the expenses for the period 2015–2018 paid by the NHIF for the health insured persons includes the following ICD codes – M80.0, M80.1, M80.2, M80.3, M80.4, M80.5, M80.8, M81.0, M81.1, M81.2, M81.3, M81.4, M81.5, and M81.8 combined to diagnose osteoporosis.

Official data for the number of patients and costs of osteoporosis pharmacotherapy in RNM were collected from the Health Insurance Fund (<http://www.fzo.org.mk/default-mk.asp>), subdivision “Consumption of drugs” from the list of drugs by generics for the period 2015–2018.

Information on the number of patients and reimbursement amount in RBG was also taken from the site of NHIF of the RBG (<https://www.nhif.bg>) and the registers of National Council on Prices and Reimbursement of Medicinal Products (NCPR) (<https://portal.ncpr.bg/register/pages/register/list-medicament.xhtml>).

Data for the reimbursed prescriptions in the RNM were taken from the information system of NHIF, for medicines purchased from pharmacies and reimbursed by the Fund for the period from 2015 to 2018.

Reimbursed costs every year were presented in absolute value, % of the total cost, and % change in comparison with the previous year.

The prescribed medicines were analyzed by INN and pharmaceutical dosage form. It was also calculated the % of the total cost for every INN paid by both NHIF, as well as the % change in every year in comparison with the previous one.

Results

Drugs used for the treatment of osteoporosis, reimbursed by the National Health Insurance Fund in the Republic of North Macedonia

According to the Law for Health Insurance (State Gazette 25/ March, 2000, last amended State Gazette 113/ July, 2014), the NHIF in RNM is a buyer of health services that include drugs from the list of the Health Insurance Fund. The health insured persons exercise their right to receive drugs from the Fund through the pharmacies, on the basis of a prescription form given by the chosen doctor of medicine, in accordance with the legal provisions and the contractual provisions of the Fund.

The reimbursed drugs in RNM are classified into two main groups: List A – List of medicines for primary health care (pre-hospital care) and List B – medicines for hospital care. The medicines from the List – A are paid by the NHIF in RNM and are prescribed on a prescription form sent for implementation in pharmacies that have a contract with the NHIF of RNM for outpatient care. One patient could receive one prescription per one medicine.

Reimbursable price of the drug is the maximum amount that the Fund provides for a particular drug. The

reference price of the medicine is determined according to the lowest defined wholesale price of the medicines, which are put into circulation in the RNM, according to the Law on Medicines and Medical Devices, with comparative analysis of the reference prices of the funds for compulsory health insurance determined by Article 63-c of the Law for Health Insurance (Official Gazette of the R Macedonia 8/ January, 2008). The treatment of osteoporosis in RNM is paid 100% by the Health Insurance Fund.

Table 1 presents the number of prescriptions of antiosteoporotic drugs available in the Macedonian pharmacies and paid by NHIF for the period from 2015 to 2018. In general, the number of prescriptions is increasing from 218 to 256 thousands of Rp per year. The largest number of prescriptions was granted in 2018 for *ibandronic acid*, followed by *cholecalciferol* (20.000 IU/ ml oral drops and the combination *alendronate sodium/cholecalciferol*. The highest percent of prescriptions belongs also to *ibandronic acid* tablets 150 mg with a declining tendency of prescribing from 41 to 39% during 2015–2018. The second most often prescribed drug is *cholecalciferol* oral drops (20.000 IU/ ml) from 21 to 25% of all prescriptions. If we add the prescriptions for the dosage form of 4.000 IU/ml it still is the second one in the list of the most often prescribed. All other medicines fall below 10% of all prescriptions.

The costs of the NHIF for the individual drugs used for the treatment of osteoporosis in R. N. Macedonia by years are presented in Table 2. Total cost is increasing from 1 to 1,2 mln Euro during 2015–2018 year. *Ibandronic acid* is the costliest accounting for 61% to 56% of the total cost with declining tendency. The cost for fixed dose combination *alendronate sodium/cholecalciferol* is constantly increasing from near 16% to 24% of total cost in 2018 year, followed by *alendronate sodium* monocompound that is declining from near 7% to 4% of the total cost for osteopathic medicines in RNM (Table 2).

The calculated average cost per prescription is almost steady for the period around 4,5 Euro (Table 2).

For the investigated period the NHIF of RNM has paid the largest amount (2 547 725.9 euro) for *ibandronic acid* tablets (150 mg) (Table 2). From the analysis by years, it is visible that the use of the drug in 2015 and 2016 was lower. 619,725.16 and 618,502.60 euro respectively were reimbursed for it. In 2017 and 2018, the use of this drug increased and the reimbursement value reached 654,466.95 and 654,649.97 euro, respectively (Table 2).

The combination of *alendronate sodium/ cholecalciferol* tablets (70 mg/ 5.600 IU) is on the second place with a total reimbursement value of 911,561.24 euro. For the *cholecalciferol* oral drops (20.000 IU/ml) the NHIF reimbursed 258,292.47 euro for the period 2015–2018 (Table 2).

The bisphosphonate *alendronate sodium* (tablets 70 mg) is on the 4th place with a total reimbursement value of 224,164.85 euro (Table 2). It is noteworthy that the cost of *alendronate sodium* decreased. In 2015, the cost was 68,190.66 euro, and in 2018 this amount decreased to 47,241.56 euro (Table 2), which is a consequence to the reduced use of the drug most likely due to the specific application conditions of *alendronate sodium* and its low oral bioavailability.

Table 1. The number of prescriptions issued for the treatment of osteoporosis and paid by the NHIF in the RNM.

INN and dosage form	2015	% of all Rp in 2015	2016	% of all Rp in 2016	% change (2016 to 2015)	2017	% of all Rp in 2017	% change (2017 to 2016)	2018	% of all Rp in 2018	% change (2018 to 2017)	Total № Rp	% of all Rp for the period
Alendronate sodium + cholecalciferol tabl. (70 mg + 5.600IE)	18465	8,47	26678	11,64	144,48	27425	11,24	102,80	31589	12,32	115,18	104157	10,99
Alendronic acid tablets (70 mg)	9920	4,55	8342	3,64	84,09	7449	3,05	89,30	6868	2,68	92,20	32579	3,44
Calcitriol caps. (0.25mcg)	1053	0,48	1150	0,50	109,21	1135	0,46	98,70	1169	0,46	103,00	4507	0,48
Calcitriol caps. (0.50 mcg)	1288	0,59	1421	0,62	110,33	1461	0,60	102,81	1327	0,52	90,83	5497	0,58
Calcium carbonate tabl. (1 g)	20910	9,59	23168	10,11	110,80	24423	10,01	105,42	26178	10,21	107,19	94679	9,99
Clodronic acid caps. (400 mg)	152	0,07	121	0,05	79,61	115	0,05	95,04	86	0,03	74,78	474	0,05
Cholecalciferol oral drops (20,000 IU/ ml)	45640	20,94	47670	20,79	104,45	54946	22,51	115,26	64435	25,13	117,27	212691	22,44
Cholecalciferol oral drops (4.000 IU/ml)	30151	13,83	30722	13,40	101,89	31946	13,09	103,98	29596	11,54	92,64	122415	12,92
Ibandronic acid tablets (150 mg)	90136	41,36	89972	39,25	99,82	95199	39,00	105,81	95173	37,12	99,97	370480	39,09
Risedronic acid tablets (35 mg)	217	0,10		0,00	0,00		0,00					217	0,02
Calcitonin nasal spray (200.000 IU/ ml)	15	0,01		0,00	0,00		0,00					15	0,00
Total number of prescriptions	217947	100,00	229244	100,00	105,18	244099	100,00	106,48	256421	100,00	105,05	947711	100,00

Table 2. Costs (in euro) paid by the NHIF in RNM for antiosteoporotic medicines by year.

INN dosage form	2015	% of all cost in 2015	2016	% of all cost in 2016	% change (2016 to 2015)	2017	% of all cost in 2017	% change (2017 to 2016)	2018	% of all cost in 2018	% change (2018 to 2017)	Total	% of total cost
Alendronate sodium/ cholecalciferol tabl. (70 mg/ 5.600 IU)	161511,3	15,85	233357,14	21,52	144,48	239895,12	21,17	102,80	276491,86	23,56	115,26	911561,24	20,67
Alendronic acid tabl. (70 mg)	68190,66	6,69	57345,59	5,29	84,10	51197,17	4,52	89,28	47241,56	4,03	92,27	224164,85	5,08
Calcitriol caps. (0.25mcg)	4413,4	0,43	4 819,82	0,44	109,21	4 757,00	0,42	98,70	4 903,34	0,42	103,08	19102,763	0,43
Calcitriol caps. (0.50 mcg)	8749,42	0,86	9653,21	0,89	110,33	9 924,62	0,88	102,81	9 015,74	0,77	90,84	37558,756	0,85
Calcium carbonate tabl. (1g)	40 237,15	3,95	44 567,94	4,11	110,76	46 932,86	4,14	105,31	50 326,93	4,29	107,23	182293,15	4,13
Clodronic acid caps. (400 mg)	17 614,16	1,73	14 021,74	1,29	79,60	13 298,48	1,17	94,84	9 971,89	0,85	74,99	55084,912	1,25
Cholecalciferol oral drops (20 000 IU)/ml	55 364,10	5,43	57 827,04	5,33	104,45	66 653,25	5,88	115,26	78 211,72	6,67	117,34	258292,47	5,86
Cholecalciferol oral drops (4 000 IU)/ml	43 430,71	4,26	44 249,65	4,08	101,89	46 015,33	4,06	103,99	42 656,21	3,64	92,70	176570,18	4,00
Ibandronic acid tabl. (150 mg)	619 725,16	60,80	618 502,60	57,04	99,80	654 466,95	57,76	105,81	654 649,97	55,79	100,03	2547725,9	57,76
Total reimbursement value	1 019 236,09	100,00	1 084 344,73	100,00	106,39	1 133 140,78	100,00	104,50	1 173 469,00	100,00	103,56	4410701,5	100,00
N of osteoporotic prescriptions	217947		229244			244099			256421			947711	
Average cost per osteoporotic Rp	4,68		4,73			4,64			4,58			4,65	

Calcium carbonate 1g is prescribed alone or in combination with other drugs, as additional therapy for the prevention and treatment of osteoporosis. For Calcium carbonate 1g 182,293 euros were reimbursed (Table 2). Costs were increased slightly but steadily over the years. In 2015, the reimbursement value was 40,237.15 euro. In the following years there was an increase in the use of the drug and in 2018 the reimbursement value paid by the NHIF increased to 50,326.93 euro (Table 2).

For clodronic acid 400 mg NHIF reimbursed 55,084.912 euros for the period from 2015 to 2018 (Table 2). The use of clodronic acid, as well as alendronic acid, has also decreased over the years. In 2015, NHIF reimbursed an amount of 17,614.16 euro, while in 2018 the reimbursement value decreased almost twice, to 9,971.89 euro.

Calcitriol 0.25 mcg and calcitriol 0.50 mcg were also prescribed for the treatment of osteoporosis and a total of 19,102.76 and 37,558.76 euros respectively were spent for

them, for the period 2015–2018 (Table 2). *Cholecalciferol* drops for oral use (4.000IU / ml) were also classified in the present analysis and prescribed for the treatment of osteoporosis. The total reimbursement value for the period 2015–2018 was 176,570.18 euro (Table 2).

Table 3, presents the reimbursement value paid by the NHIF for all drugs in comparison with the cost for the antiosteoporotic drugs in RNM. It is visible that during the years of the study period, the reimbursement value increased from 1,019,236 euro paid in 2015, to 1,173,469 euro, paid in 2018 but the percent of total cost remains steady around 2,5% out of the total NHIF budget for medicines.

Table 3. Reimbursed costs paid by the NHIF in the RNM.

	2015	2016	2017	2018
Total reimbursement value for all drugs (in €)	39,472,098	42,734,219	45,337,420	45,559,918
Reimbursement amount paid for antiosteoporotic drugs (in €)	1,019,236	1,084,344	1,133,141	1,173,469
% of the amount reimbursed for antiosteoporotic drugs	2,58%	2,54%	2,5%	2,56%

Drugs used for the treatment of osteoporosis, reimbursed by the NHIF in the Republic of Bulgaria

Similar to RNM in RBG the NHIF is a buyer of health services that include medicines from the list of the NCPR (<https://portal.ncpr.bg/registers/pages/register/list-medicament.xhtml>). The health insured persons receive prescriptions from their family physician for one or 3 months for their ambulatory therapy (National People Assembly. Law for health insurance, State Gazette 70/ 19 June, 1998, last amended State Gazette 54/ 16 June 2020).

The reimbursed medicines in RBG are classified into three main groups: Annex 1 – List of medicines for outpatients paid by the NHIF, Annex 2 medicines for hospital care paid by the hospital budgets or by the NHIF, and Annex 3 – list of medicines for infectious diseases and vaccines covered by the Governmental budget. One patient could receive one prescription per three medicines

for the therapy of one ICD code of the disease (Ministry Council, Decree on conditions, rules, and order of regulation and registration of prices of medicinal products. State Gazette 40/30 April 2013; last amended State Gazette 19/ 6 March 2020).

Reimbursable price of the medicines is settled as the lowest price per define daily dose (DDD), out of all trade names and dosage forms belonging to the same INN. The treatment of osteoporosis in Bulgaria is reimbursed 50% by the Health Insurance Fund.

As can be seen in Table 4, the largest number of patients was registered with a diagnosis of M81.0 or “Osteoporosis after menopause”. Their share increased from 76 to 78% of all osteoporotic patients suggesting that the prevailing part of the patients are female (Table 4). The relative share of the peoples with OP with pathological fractures (ICD M80.0) is decreasing as part of all patients from 18% to 16% but the crude number of people and the respective trend is increasing from 2% in 2016 in comparison with 2015 to 8% in 2018 in comparison with 2017 (Table 4).

In 2015, the total number of patients with OP after menopause (ICD M81.0) was 13443 (Table 4) people, for whose treatment the health care fund reimbursed a total amount of 1,363,802 euro, and in 2018 the total number of patients was 18523 with a reimbursement amount paid by the NHIF 2,265,654.30 euro (Table 5). Comparing the number of patients with a complication of pathological fracture and the cost of treatment paid by the NHIF, it was found that the NHIF has paid for medicines 291,149.28 euro in 2015 and reached 501,686.09 euro in 2018 for the diagnosis M80.0 “Osteoporosis with a pathological fracture after menopause” (Table 5). Logically the cost of therapy of ICD M81.0 is the highest one accounting to 76% on average during the observed period. Second costly is the ICD M80.0 OP with pathological fractures accounting for 17% of total cost on average.

The total number of patients with osteoporosis in 2015 was 17691 people and increased to 23621 persons in 2018 (Table 4), for whose treatment the amount of 1,764,327.27 and 2,994,563,26 euro was reimbursed, respectively (Table 5).

Table 4. Number of health insured persons (HIP) for the period 2015–2018 for the sections with ICD codes M80 and M81 in the RBG.

ICD codes	ICD code name	2015	% of all patients in 2015	2016	% of all patients in 2016	% change (2016 to 2015)	2017	% of all patients in 2017	% change (2017 to 2016)	2018	% of all patients in 2018	% change (2018 to 2017)
	Total	17691	100	19200	100	108,53	21307	100	110,97	23621	100	110,86
M80.0	OP with pathological fracture after menopause	3188	18,02	3271	17,04	102,60	3489	16,37	106,66	3772	15,97	108,11
M80.1	OP with pathological fracture after ovariectomy	255	1,44	248	1,29	97,25	273	1,28	110,08	276	1,17	101,10
M80.2	Immobilization OP with pathological fracture		0,00		0,00		1	0,00		2	0,01	200,00
M80.4	Drug-induced osteoporosis with pathological fracture	1	0,01	13	0,07	1300,00	14	0,07	107,69	6	0,03	42,86
M80.5	Idiopathic osteoporosis with pathological fracture	3	0,02	2	0,01	66,67	2	0,01	100,00	1	0,00	50,00
M80.8	Another osteoporosis with a pathological fracture	104	0,59	100	0,52	96,15	142	0,67	142,00	179	0,76	126,06
M81.0	OP after menopause	13443	75,99	14866	77,43	110,59	16631	78,05	111,87	18523	78,42	111,38
M81.1	OP after ovariectomy	334	1,89	346	1,80	103,59	339	1,59	97,98	349	1,48	102,95
M81.2	Immobilization OP	5	0,03		0,00	0,00		0,00		1	0,00	
M81.4	Drug-induced osteoporosis		0,00		0,00		1	0,00			0,00	0,00
M81.5	Idiopathic osteoporosis	11	0,06		0,00	0,00		0,00			0,00	
M81.8	Other osteoporosis	347	1,96	354	1,84	102,02	415	1,95	117,23	512	2,17	123,37

Table 5. Costs for the period 2015–2018 for the sections with ICD codes M80 and M81 in the RBG.

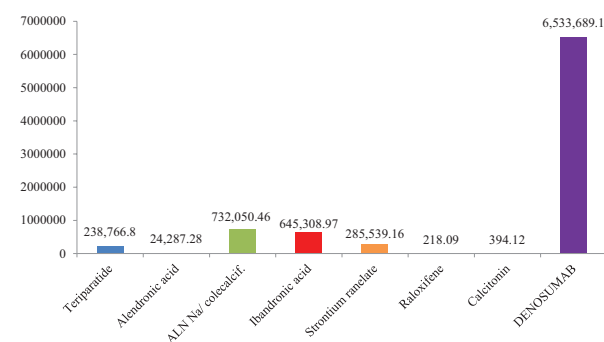
ICD codes	2015	% of all cost in 2015	2016	% of all cost in 2016	% change (2016 to 2015)	2017	% of all cost in 2017	% change (2017 to 2016)	2018	% of all cost in 2018	% change (2018 to 2017)
M80.0	291149,28	16,50	376993,66	17,86	129,48	482512,46	18,85	127,99	501686,09	16,75	103,97
M80.1	16643,18	0,94	19649,40	0,93	118,06	24777,17	0,97	126,10	62227,02	2,08	251,15
M80.2		0,00		0,00		1672,84	0,07	#DIV/0!	2452,86	0,08	146,63
M80.4	446,67	0,03	11577,18	0,55	2591,89	16313,41	0,64	140,91	4182,87	0,14	25,64
M80.5	2,55	0,00	1760,14	0,08	69025,10	2661,64	0,10	151,22	352,23	0,01	13,23
M80.8	15349,63	0,87	16892,30	0,80	110,05	25694,51	1,00	152,11	35187,91	1,18	136,95
M81.0	1363802,00	77,30	1592256,00	75,45	116,75	1901723,00	74,31	119,44	2265654,30	75,66	119,14
M81.1	22622,44	1,28	28041,18	1,33	123,95	29069,29	1,14	103,67	32399,15	1,08	111,45
M81.2	7,15	0,00		0,00	0,00		0,00		703,95	0,02	
M81.4		0,00		0,00		1056,18	0,04			0,00	0,00
M81.5	16,34	0,00		0,00	0,00		0,00			0,00	
M81.8	54288,03	3,08	63246,96	3,00	116,50	73707,72	2,88	116,54	89716,88	3,00	121,72
Total	1764327,27	100,00	2110416,82	100,00		2559188,22	100,00		2994563,26	100,00	

The most commonly used medicines in Bulgaria for the treatment of osteoporosis and included in Annex 1 of the Positive Drug List – Medicinal products intended for the treatment of diseases, which are paid for under the Health Insurance Act are presented in Table 6 and Fig. 1. The total amount paid by the NNIF only for drugs in 2015 was 1,559,301,47 euro and reached 2,765,761.31 euro in 2018, which presents an almost 100% increase in the costs (Table 6).

It was found that the highest costs were spent on the monoclonal antibody *denosumab*, for which NHIF has paid 6,533,689.10 euro over a period of 4 years. The analysis of the value for *denosumab* for each year separately (Table 6) shows that the dynamics of costs were progressively increasing. From 1,055,097.20 euro in 2015 the costs doubled to 2,291,197.67 euro in 2018. It also increases as the relative share of the total cost paid for osteoporosis from 68 to 83% in 2018. Mostly evident is the increase in sales in 2017 comparing with 2016 when the rise of more than 2000% is pointed out (Table 6).

From the analysis of the drug use for osteoporosis in Bulgaria (Table 6), it was found that *strontium ranelate* was reimbursed 127,123.61 euro in 2015 and after this period the use of the drug sharply decreased due to side effects. The European Medical Agency (EMA/10206/2014) recommends limiting the use of *strontium ranelate* in patients with cardiovascular disease (Bolland and Grey 2016). Concerns about cardiac safety have led to a new contraindication to strontium ranelate in patients with uncontrolled hypertension and/or current or past history

of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease. But this medicine remains a useful therapeutic alternative in patients with severe osteoporosis without cardiovascular contraindications who are unable to take another osteoporosis treatment (Register 2014). For the period of 4 years, the total reimbursement amount that the NHIF has paid for this drug was 285,539.16 euro (Fig. 1).

**Figure 1.** Total reimbursement value for antiosteoporotic drugs, granted under the NIHF in the RBG (2015–2018).

For the drug *teriparatide*, the Bulgarian NHIF reimbursed a total of 238,766.8 euro for the period of 4 years (Fig. 1). The analysis by years shows that the cost paid by the NHIF of the drug increased from 1,935.32 euro in 2015 to 153,385.46 euro in 2017. As relative share this increase is from 0.12% in 2015 to 4.37 in 2016, to 6.51% in

Table 6. Cost (in euro) paid by the NHIF of RBG by year for antiosteoporotic drugs.

Drug (INN)	2015	% of all cost in 2015	2016	% of all cost in 2016	% change (2016 to 2015)	2017	% of all cost in 2017	% change (2017 to 2016)	2018	% of all cost in 2018	% change (2018 to 2017)
Teriparatide	1935,32	0,12	83446,02	4,37	4311,74	153385,5	6,51	183,81	130485,42	4,72	85,07
Ibandronic acid	214645,75	13,77	160117,32	8,39	74,60	139315,9	5,91	166,95	131229,99	4,74	94,20
Calcitonin	279	0,02	115	0,01	41,22	–	–	–	–	–	–
Alendronic acid	2983	0,19	8564,43	0,45	287,11	8411,95	0,36	10,08	4328,27	0,16	51,45
Strontium ranelate	127123,61	8,15	87811,9	4,60	69,08	65813,01	2,79	78,87	4790,64	0,17	7,28
Denosumab	1055097,2	67,66	1388346,9	72,74	131,58	1799047	76,33	2155,94	2291197,7	82,84	127,36
Alendronate sodium/ colecalciferol	157050,22	10,07	180205,77	9,44	114,74	191065,2	8,11	228,97	203729,32	7,37	106,63
Raloxifene	187,37	0,01	15,36	0,00	8,20	15,36	0,00	0,02	–	–	–
Total	1559301,47	100,00	1908622,73	100,00		2357054	100,00		2765761,31	100,00	

2017 and drop to 4,72% in 2018 year. In 2018 the total amount paid by the NHIF for this drug decreased slightly and reached 130,485.42 euro.

In the Republic of Bulgaria for the treatment of osteoporosis, *raloxifene* and *calcitonin* were the least commonly used drugs, for which the NHIF has reimbursed 218.09 and 394.12 euro, respectively. Some restrictions for *calcitonin*, due to the increased risk of malignancies, are also known. In view of the new safety concerns in relation to the risk of cancer in long-term use and the limited efficacy of calcitonin in the treatment of osteoporosis, EMA is of the opinion that the benefit-risk balance of the intranasal formulations of calcitonin-containing medicinal products is not positive under normal conditions of use. Therefore the Committee recommended the suspension of the Marketing Authorisations for the intranasal formulation of calcitonin. EMA recommends do not use it in osteoporosis (EMA/109665/2013), which affects its consumption in Bulgaria. Since 2016, the sale of *calcitonin* (salmon synthetic) in RBG has been suspended. EMA therefore considered the benefit-risk balance of injectable calcitonin-containing products for the treatment of Paget's disease, for the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, and for the treatment of hypercalcaemia of malignancy for the shortest possible time using the minimum effective dose (EMA/109665/2013).

Concerning the use of bisphosphonates in the RBG for the period 2015–2018, it was established that the use of *alendronic acid* (tablets of 70 mg) throughout the period was very low. During the same period, the use of the other two drugs *alendronate sodium/cholecalciferol* tablets (70 mg/ 5.600 IE) and *ibandronic acid* (tablets 150 mg and solution for injection, 3 mg/ 3 ml) was higher. The use and the reimbursement value of the drug *alendronate sodium/cholecalciferol*, increased over the years from 157,050.22 euro in 2015 to 203,729.32 euro in 2018. With *ibandronic acid*, a different situation was observed. Its use, respectively reimbursement value decreased over the years. In 2015 214,645.75 euros were reimbursed and by 2018 the value was decreased to 131,229.99 euro (Table 6).

Comparative analysis

Comparative analysis of the reimbursement policy and financing the anti-osteoporotic medicines between RBG and RNM revealed some similarities as well as differences.

On the first place in both countries the access to anti-osteoporotic medicines is granted via the reimbursement system although the level of reimbursement is higher in RNM (100%) and lower in RBG (50%).

It was found that in Bulgaria, as well as in Macedonia, the number of people suffering from osteoporosis is progressively increasing during the years of the study period, which leads to an increase in the cost of treatment of this disease, paid by the health insurance fund.

Comparing to RBG, the NHIF of RNM has reimbursed a higher value for bisphosphonates for the period

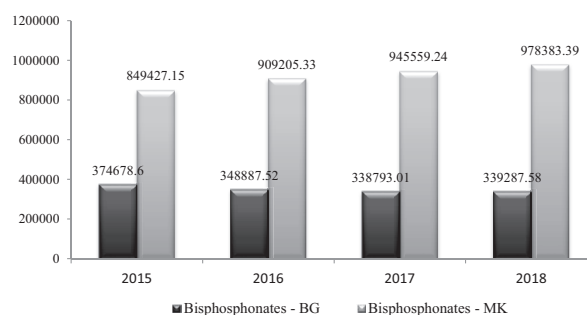


Figure 2. The total reimbursement amount for the three bisphosphonates paid by the NHIF in the RBG and RNM (2015–2018).

2015–2018 (Fig. 2). Probably this difference is due to the higher reimbursement rate for osteoporosis drugs in Macedonia – 100%.

Bisphosphonates *alendronic acid*, *alendronate sodium/cholecalciferol* and *ibandronic acid* tablets of 150 mg were dispensed under the NHIF in both countries. In Bulgaria, the NHIF provides also *ibandronic acid* solution for injection, 3 mg/ 3 ml.

The NHIF of RBG reimbursed a total of EUR 1,401,646.71 for that three BP for the period 2015–2018. During the same period, the NHIF of RNM reimbursed a total of EUR 3,682,575.11 for these medicines. We might suppose that the prices of medicines are also higher but this needs further evaluation. The use of bisphosphonates in the RNM has been constantly increasing over the years, while in Bulgaria the use of bisphosphonates has slightly decreased or remained relatively constant for the last two years of the analysis.

The lower costs of the NHIF in Bulgaria for bisphosphonates, compared to RNM, are most likely due to the huge costs for *denosumab*, as well as due to the lower rate of reimbursement by the NHIF for ICD-osteoporosis – 50% compared to 100% in Macedonia.

Denosumab has not been registered in Macedonia, but it was approved for placing on the market in certain cases according to article 31 (Chapter III.I Marketing authorization) of the Law on Medicines and Medical Devices (Official Gazette of RM 106/ September 2007), in exceptional cases and justified reasons related to the health of patients (rare diseases, ethical aspects, vital hazardous diseases), if appropriate medication is not available, it may issue a conditional marketing authorization containing obligations for the holder of the approval, and for the longest period of one year.

Unlike Macedonia, *vitamin D* derivatives and *calcium* products, widely used in our western neighboring country, are not reimbursed in Bulgaria for the treatment of osteoporosis whereas *strontium ranelate*, *teriparatide* and *raloxifene* are not reimbursed in RNM.

Discussion

Similarly, to other studies, we found that the cost of osteoporosis pharmacotherapy is constantly rising (Fleurence

et al. 2006; Burges et al. 2007; Savova et al. 2012). Other authors pointed out that the larger is the cost of fractures therapy (Savova et al. 2012) but we did not explore these costs that might be considered as one of the limitations of our study. The fact that the denosumab is responsible for the highest reimbursed cost in Bulgaria is not surprising having in mind that biological therapy is costly all over Europe. (Kawalec et al. 2017).

It is also evident that despite the 3 times higher population (around 7 mln Bulgarians in 2018/ just over 2 million North Macedonians) the total cost of pharmacotherapy in RBG is twice bigger than the cost in RNM. This could be explained with the reimbursement policy and high percent of reimbursement of medicines in RNM. Probably the prices are also higher in RNM because less reimbursed medicines account for high value but this factor was not explored in our study. The reason is the difference in the formation of the prices and in the reimbursement.

Regarding the reimbursed medicines we might say that the policy of RNM is more restrictive and fewer INN are reimbursed. Bulgarian therapeutic practice includes *teriparatide*, *denosumab*, *strontium ranelate* that later was excluded, and other molecules while the practice in the RNM is more bisphosphonates oriented.

The new moments that this study adds are two. The first one is the comparison of reimbursement policy and cost between two neighboring countries with lots of similarities in the reimbursement policy (Brodzky et al. 2019). To our knowledge, this is the first comparative analysis between RNM and RBG in the area of anti-osteoporotic medicines. The second is that this is also one of the first cost studies for osteoporosis in RNM. Comparing both countries it is useful to analyse the cost tendencies, explain possible reasons and change the reimbursement policy if necessary.

The other limitation of our study is the fact that we could not compare the number of patients by ICD codes due to the different reporting of the number of patients in RBG and RNM. The same concerns also and the prescriptions reporting that is missing in Bulgaria.

Conclusions

The number of patients and cost of pharmacotherapy in RNM and RBG are increasing but the reimbursement policy in RNM is more restrictive in terms of the number of reimbursed medicines. On the other side, the RNM is with a higher level of reimbursement that might positively affect the cost of pharmacotherapy.

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