

ANALYSIS OF CARDIOVASCULAR MEDICINES PRICES AND REIMBURSEMENT IN BULGARIA AND ROMANIA

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Abstract

The goal of the study was to compare the pricing methodology, manufacturers, and retail prices of cardiovascular medicines (CV), reimbursed in Bulgaria (BG) and Romania (RO). Regulatory analysis was applied towards the several legislation acts enforced in BG and RO, corresponding to the pricing system. The price comparison was made for all reimbursed cardiovascular medicines (mono-products and fixed dose combinations). Descriptive statistic and t-test analysis was used to determine the differences in average manufacturer and retail prices per International Non-proprietary Name (INN). Overall, this study reveals that, despite the fact that both countries joined the European Union simultaneously, and follow the same European regulations, decisions on what reimbursement approach to take is left to the national policy, leading to differences in patient co-payment, manufacturer and retail prices, and influencing both pharmaceutical industry and patients' access to medicines.

Rezumat

Scopul cercetării este de a se efectua o comparație între metodologia stabilirii prețurilor de producție și a prețurilor de vânzare cu amănuntul ale medicamentelor destinate afecțiunilor cardiovasculare, compensate în Bulgaria și România. Cu privire la legislația care a intrat în vigoare la mijlocul anului 2015 în Bulgaria și respectiv în 2009 în România, a fost aplicată o analiză de reglementare. A fost efectuată o comparație a prețurilor pentru toate produsele medicale pentru sistemul cardiovascular (produse mono și combinații de doze fixe). Pentru determinarea diferențelor cu privire la prețurile medii de producție și prețurile de vânzare cu amănuntul pentru DCI-uri (Denumiri comune internaționale) au fost utilizate statistica descriptivă și testul t Student. Studiul dezvăluie că, în ciuda faptului că ambele țări au aderat la Uniunea Europeană simultan și respectă reglementările europene comune, deciziile legate de alegerea metodei de compensare sunt luate de politica națională, ceea ce duce la diferențe legate de co-plată pacientului, prețurile de producție și prețurile de vânzare cu amănuntul și influențează atât industria farmaceutică, cât și accesul pacienților la produsele medicale.

Keywords: Bulgaria, Romania, legislation, pricing and reimbursement system, cardiovascular medicines

Introduction

On January 1st, 2007, Romania (RO) and Bulgaria (BG) joined the European Union (EU). Before their accession, the two nations had to implement wide-ranging political, economic and legal reforms, including modernization of their healthcare and pharmaceutical industries. This also includes the harmonization of the pharmaceutical legislation [7].

Until 2000, Romania and Bulgaria were among the poorest performing economies of Central and Eastern Europe (CEE). The turnaround in 2000 was preceded by a protracted and precipitous decline in Gross Domestic Product (GDP), a peaking of the poverty rate to near 36%, and inflation of above 54% per year. EU accession aspirations and the opening of official entry negotiations with the EU in December 1999 spurred both countries' commitment to reforms. This led to significant macroeconomic consolidation and impressive growth in recent years [3].

According to research from Eurostat, national minimum wages in the European Union (EU) ranged from €184 per month in Bulgaria to €1923 in Luxembourg. From 2008 to 2015, a national minimum wage expressed in national currency, increased in every Member State. The highest increases were registered in Romania (+95%), Bulgaria (+64%), Slovakia (+58%), and Latvia (+57%) [2]. Nevertheless still wages in CEE remain the lowest ones in the EU.

In parallel with other changes, the pharmaceutical market continued to grow. Purcarea *et al.* [15] evaluating Romanian market, found that despite extremely difficult conditions for pharmaceutical companies, the Romanian market is growing, even in the context of the global economic decline. Pharmaceutical sales in terms of volume in CEE are still being dominated by generic medicines, due to low *per capita* income and underinvestment in

development of new medicines. Pharmaceutical producers in the region kept their focus on the manufacturing of low-cost generic medicines with major companies, generating the bulk of their sales revenue abroad [14, 24].

The co-payment for prescription medication in BG and RO is the highest one [6]. To cope with the low wages, rising pharmaceutical expenditures and high co-payment, the Governments are under pressure to take adequate cost-containment measures to ensure affordable medicines for the population [13, 23]. The main factors that influence the pharmaceutical industry in Romania refer to the following: chronic diseases are soaring; healthcare policy producers and payers are increasingly mandating what doctors can prescribe; pay-for-performance is on the rise; the boundaries between different forms of healthcare are blurring; governments are beginning to focus on prevention rather than treatment [16]. Price control is the measure that affects supply and demand of the medicines and many countries introduce the reference pricing system, allowing a mutual comparison between their medicines prices [1].

The goal of our study was to compare the pricing methodology, manufacturers, and retail prices of cardiovascular medicines, reimbursed in Bulgaria and Romania.

The study questions discussed in this article are referring to the: similarities and differences in the medicines price formation and control in both countries; and influence of regulatory measures on manufacturers' and retail medicines' prices with focus of the cardiovascular (CV) ones.

Materials and Methods

A regulatory analysis was performed based on the current regulations, which set the pricing rules in both countries. In order to compare structure of price calculation and reimbursement mechanism the following regulations were reviewed: Order of the Ministry of Health no. 75/2009 on approving the norms for calculating the price of medicines for human use [18]; Government Decision no. 720/2008 for approving the list of non-proprietary names corresponding to medicines that the patients benefit of, with or without personal contribution, based on prescription in the social healthcare security system [19]; Order no. 615/2010 approving the calculation of the reference price for medicines. [20]; Order № 1523 /12.16.2014 amending and supplementing the Health Ministry Order No.245 of 16 March 2012 approving the prices of products covered in the national catalog of prices for medicinal products [21]; Ordinance on the terms, rules and procedure for regulation and registration of prices for medicinal products [8] for Bulgaria.

The regulatory analysis focused on the price control measures, on the manufacturers' prices, and the price formation until the final consumer, at retail level.

For the CV medicines, a retrospective, observational and statistical analysis of the manufacturers' and retail prices of mono-products and fixed dose combinations (FDC), reimbursed in both countries, was performed. The observed medicines are included in the positive drug lists (PDL) Annex I [10] in Bulgaria and in Sub lists A, B, C [9] in Romania. We systematically reviewed the annexes of the PDLs and extracted all international non-proprietary names (INNs), trade names, and dosage forms of medicines from therapeutic groups belonging to Anatomical Therapeutic Chemical (ATC) C: calcium antagonists, β -blockers, diuretics, angiotensin-blockers, angiotensin-converting-enzyme inhibitors, and fixed doses combinations of each therapeutic groups. It was compared the manufacturer' price (without value-added tax – VAT), the final retail price (plus VAT), and the average price per INN.

The prices were then statistically processed by calculating the average price, standard deviation, using Excel analysis tool pack. Student t-tests were used to evaluate the statistical significance of the differences between compared prices. The null hypothesis was that the average manufacturer and retail prices of every INN are not statistically different between BG and RO.

On total, 31 INNs belonging to 5 ATC groups and 9 FDC were included in the analysis. We have found identical products from the same marketing authorization holder (MAH) within 18 INN. All prices are presented in EURO at the ex-change rate of 1 Euro = 1.956 BGN and 1 Euro = 4.26 RON.

Results and Discussion

Pricing and reimbursement policy

The method for calculating the prices of medicinal products is regulated by the Ministry of Health (MoH) Order no. 75/2009 [18]. The Ministry of Health (MoH) is the main regulatory authority to approve prices for medicinal products. The rules distinguish between: 1) over-the-counter (OTC) products, there is an obligation to notify the Ministry of Health (MoH) for the price of newly authorized OTCs or the changes in price within 30 days of the placement on the market of particular medicinal products; 2) prescription-only products, the MoH following the described in the ordinance methodology must approve the prices [4].

The Romanian National Health Insurance House (NHIH) (www.cnas.ro) is an independent public authority with legal status. It sets the regulations for the functioning of the social health insurance system. The Romanian National Health Insurance House

(NHIH) based on Order no. 615/2010 is approving the calculation of the reference price for medicines [4]. In 2003, the Bulgarian Drug Agency published the first Positive Drug List (PDL) of medicines. The authority that regulates pharmaceutical prices is the National pricing and reimbursement council, stipulated since April 2013.

In Bulgaria and Romania, price regulation of pharmaceuticals uses external reference pricing. In Romania MoH sets the producer price as the lowest price among the 12 reference European countries. (Order no. 75/2009). The price from the country of origin shall be considered when no price is set in the 12 countries (Figure 1). According to the price legislation in Bulgaria, a pharmaceutical's ex-manufacturer price proposed by the producer or MoH cannot be higher than the lowest price among other 10 reference European countries. When there is no price available in one or more of the reference countries, or when the price is not approved in all reference countries, the price is set using the same method with 7 additional reference countries (Figure 1). Figure 1 suggests that 9 of the countries used as reference are the same in Bulgaria and Romania, with both countries also being a reference for each other. The price revisions in one country may contribute to changes in the other.

The price calculation methodology in the countries is as follows: in Bulgaria: (manufacturer price + VAT) + (wholesale margin + VAT) + (retail margin over the manufacturer price + VAT); in Romania:

(manufacturer price) + (wholesale margin) + (retail margin over the wholesale price) + VAT.

A regressive margin scale is used in both countries. Table I presents established margins at all levels according to approved manufacturer price. For the most expensive medicines, both countries control not only margins but also state maximum allowed amount. At the end, the upper limit retail price is calculated and prices are published.

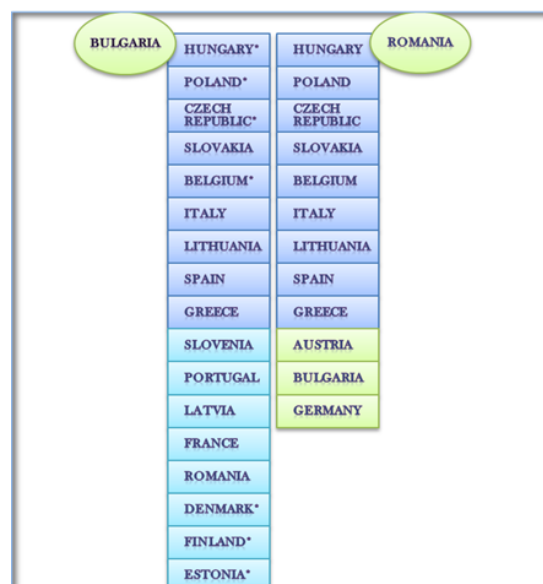


Figure 1.

Reference baskets with main and additional (*) reference countries

Table I
Regressive margin scale and VAT

Bulgaria		Romania	
Manufacturer price (euro)	Maximal wholesale margin, %	Manufacturer price (euro)	Maximal wholesale margin, %
Maximal Wholesale margins			
0 - 5	7%	0 - 11	14%
5 - 15	6%	11 - 22	12%
Over 15	4%, but no more than 5 euro	22 - 67	10%
		Over 67	7 euro
Producer price (euro)	Maximal retail margin, %	Wholesale price (euro)	Maximal retail margin, %
0 - 5	20%	0 - 5	24%
5 - 15	18%	5 - 11	20%
Over 15	16%, but no more than 12.5 euro	11 - 22	16%
		22 - 67	12%
		Over 67	8 euro
Value Added Tax - VAT, %			
20		9	

The difference between the two methodologies is not only in the wholesale, retail mark-up rates and rate of VAT but also in the fact that in Bulgaria retail margin is added on to the ex-manufacturer price, unlike Romania where retail margin is added on to the wholesale price.

When we compare the regressive margin scale, it is obvious that in both countries, manufacturer prices are established as lower out of the reference countries, while the wholesale margin in Romania (14 %) is twice higher than in Bulgaria (7%). The retail margin in Romania (24 %) is also higher than in Bulgaria (20%).

In the pricing regulation is stipulated that the prices of generic medicines should not exceed 65% to 70% of the price of the equivalent in Romania [12]. If the price of the generic is lower than 65%, the originator should decrease its price, so as the difference with generic to be no more than 35%. The manufacturer prices are an object of revision and approval every year. The procedure can take a maximum of 90 days, but it can be extended if the Ministry of Public Health [5, 18] requires more information.

Manufacturer price of the first generic product in Bulgaria should not exceed 80% from the price of the originator. The National Council of pricing and reimbursement of medicinal products (NCPRMP) updates PDL twice per month [8]. It could be considered that the national legislation provides competitive advantages to the generic medicines. The prices of the medicinal products with one product per INN are checked every six months, while the prices in INNs where both branded and generic exist are checked every twelve months.

In order to be included in the reimbursement list in Romania, the INN of the respective medicinal products must have been reimbursed in at least three EU Member States for a minimum of 1 year, and have to meet certain efficacy and safety requirements. The National Health Insurance House sets the regulations for the functioning of the social health insurance system and regulates certain aspects in connection with the reimbursement of medicinal products. There are two stages in calculating the reimbursement price: the reference price of the medicinal product must be determined; the reimbursement price is determined as a percentage of the reference price and depends on its listing.

The approved lists are set out in Government Decision no. 720/2008 and the percentage is as follows: *Sublist A* (90%) includes mainly generics, which are considered as important, and cost-effective (essential medicines); *Sublist B* (50%) includes medicines that are judged as less cost-effective; *Sublist C* (100%) includes medicines for outpatient care for a group of diseases, included in National Health Programs, paediatric medicines and medicines used in pregnancy. *List C* is divided into three sub-lists, all of which are 100% reimbursed [4, 5].

The National Catalogue of Prices of Medicines Authorized for Placement on the Market in Romania (CANAMED) contains the maximum prices (manufacturer, wholesale and retail) approved by the MoH.

The reimbursed medicines in Bulgaria are listed in 3 annexes of the PDL, according to the payer institution [8]. The obligatory requirement for reimbursement is that INN should be paid in public funds in at least 5 of the above mentioned 17 reference countries. National Council on Pricing and Reimbursement defines reimbursement level *per* INN, and it is 25%, 50% or 100% for mono-products and 50% for all fixed doses combinations. This applies only to Annex I – medicines for ambulatory care. Annexes II and III include medicines, for hospital care and medicines for socially important diseases (AIDS, infectious diseases, vaccines etc.), respectively. All the products in Annexes II, III are reimbursed 100 %.

Comparison of CV medicines prices

CV diseases are the leading cause for morbidity and mortality in both countries under consideration and therefore medicines for their therapy should always be available and affordable [11]. This is the reason to choose CV medicines in our second part of the study. Although the generic cardiovascular medicines reimbursed in Bulgaria and Romania belong to the same 5 CV therapeutic groups, a difference exists in other compared indicators. Comparison by INN benefits BG ($n = 25$), while in RO there are $n = 24$ INNs, and out of them 9 are FDCs. Dosage forms in BG are 64 and 66 in RO, while trademarks are 448 in BG and 532 in RO. The overlapping products are $n = 129$ (Tables II-VII).

In the class of calcium antagonists, the dosage forms of products reimbursed in Romania are the same as Bulgaria, but the number of reimbursed generics with INN amlodipine and felodipine in Romania is higher than in Bulgaria. Concerning verapamil, nifedipine and lercanidipine there are more generics in Bulgaria (Table II, Figure 2). The average manufacturer and retail prices of overlapping products are the same. There is no statistically significant difference for producer price regarding verapamil, felodipine, and lercanidipine ($p > 0.05$) and retail price to verapamil, lercanidipine ($p > 0.05$) (Figure 2).

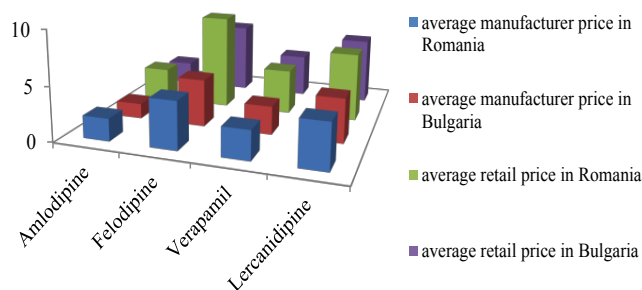


Figure 2.

The comparison of average prices in Romania and Bulgaria for the calcium antagonists group

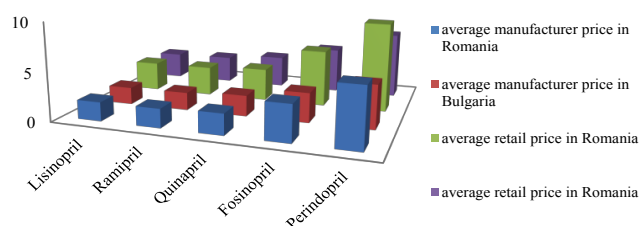
Table II

Trademarks per dosage form and reimbursed percentage per INNs for the group of calcium antagonists

		Romania	Bulgaria		Romania	Bulgaria
INN		Number of trademarks	Number of trademarks	Overlapping trademarks	Reimbursed percentage	Reimbursed percentage
Amlodipine	10 mg	17	12	4	90%	50%
	5 mg	17	14	6	90%	50%
Felodipine	10 mg	5	3	1	90%	50%
	5 mg	5	6	2	90%	50%
	2.5 mg	4	2	1	90%	50%
Nifedipine	30 mg	1	1	1	90%	50%
	20 mg	1	3	-	90%	50%
	10 mg	-	1	-	-	50%
Verapamil	40 mg	3	3	-	90%	50%
	80 mg	5	4	1	90%	50%
	240 mg	1	3	1	90%	50%
	120 mg	-	2	-	-	50%
Lercanidipine	10 mg	5	5	3	50%	50%
	20 mg	4	5	2	50%	50%

In the group of ACE inhibitors ("prils"), we observed 5 INNs. The number of generics is similar in both countries; dosage forms and trademarks reimbursed in both countries are the same for all INNs (Table III,

Figure 3). The average producer and retail prices are almost the same for quinapril. For the other products in this group, prices are lower in BG and the differences are statistically significant ($p < 0.05$) (Figure 3).

**Figure 3.**

The comparison of average prices in Romania and Bulgaria for the ACE-inhibitors group

Table III

Trademarks per dosage form and reimbursed percentage per INNs for the group of ACE inhibitors

		Romania	Bulgaria		Romania	Bulgaria
INN		Number of trademarks	Number of trademarks	Overlapping trademarks	Reimbursed percentage	Reimbursed percentage
Enalapril	5 mg	9	8	1	90%	25%
	10 mg	12	10	-	90%	25%
	20 mg	10	10	-	90%	25%
Lisinopril	2.5 mg	1	1	1	90%	25%
	5 mg	5	6	3	90%	25%
	10 mg	8	8	3	90%	25%
	20 mg	8	7	2	90%	25%
Ramipril	40 mg	1	-	-	90%	-
	2.5 mg	8	1	-	90%	25%
	5 mg	9	11	3	90%	25%
Quinapril	10 mg	9	10	3	90%	25%
	5 mg	1	-	-	90%	-
	10 mg	1	2	1	90%	25%
Fosinopril	20 mg	1	2	1	90%	25%
	10 mg	3	3	1	90%	25%
	20 mg	3	3	1	90%	25%
Perindopril	2 mg	1	-	-	50%	-
	4 mg	6	5	2	50%	25%
	5 mg	1	2	1	50%	25%
	8 mg	6	5	2	50%	25%
	10 mg	2	2	2	50%	25%

Within the group of β -blockers, the number of dosage forms is almost the same, except atenolol (Figure 4). There are overlapping products with INN bisoprolol, nebivolol and carvedilol, which are reimbursed in both countries (Table IV). The average

manufacturer ($p = 0$) and retail prices ($p < 0.05$) for bisoprolol are equal or almost the same, respectively. The average prices for carvedilol and nebivolol are lower in BG and the difference is statistically significant ($p < 0.05$) (Figure 4).

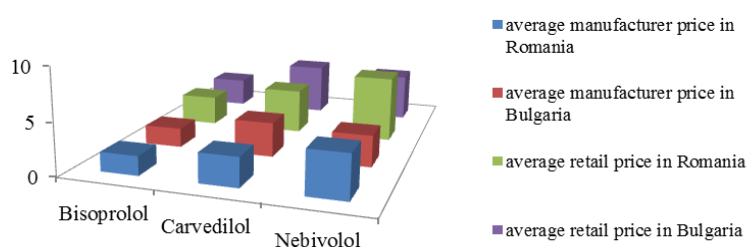


Figure 4.

The comparison of average prices in Romania and Bulgaria for the β -blockers group

Table IV

Trademarks per dosage form and reimbursed percentage per INNs for the group of β -blockers

INN		Romania	Bulgaria	Overlapping trademarks	Romania	Bulgaria
		Number of trademarks	Number of trademarks		Reimbursed percentage	Reimbursed percentage
Metoprolol	25 mg	4	1	-	90%	50%
	50 mg	13	13	-	90%	50%
	100 mg	14	12	-	90%	50%
	200 mg	1	3	-	90%	50%
Atenolol	25 mg	-	2	-	-	50%
	100 mg	5	-	-	90%	50%
	50 mg	4	3	-	90%	50%
Bisoprolol	2.5 mg	3	3	2	90%	50%
	5 mg	10	13	4	90%	50%
	10 mg	9	11	3	90%	50%
Carvedilol	6.25 mg	10	8	3	90%	50%
	12.5 mg	10	7	3	90%	50%
	25 mg	10	8	3	90%	50%
Nebivolol	5 mg	11	12	3	50%	50%

Angiotensin II receptor antagonists (sartans) are a relatively new therapeutic group. In Romania, the number of registered generics in this group is higher than in Bulgaria, and the average

manufacturer price and retail price of INNs are higher in Romania. The average prices differ statistically significant for all compared INNs. ($p > 0.05$) (Figure 5) (Table V).

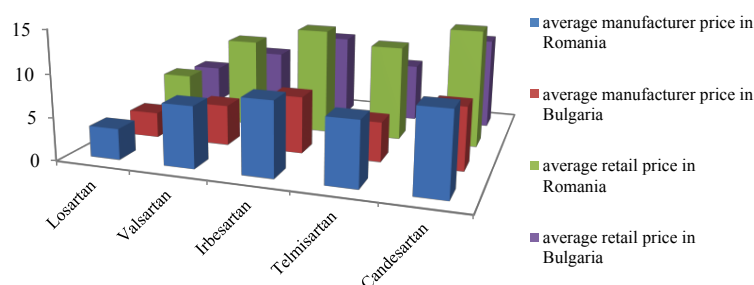


Figure 5.

The comparison of average prices in Romania and Bulgaria for the angiotensin II blockers group

Table V

Trademarks per dosage form and reimbursed percentage per INNs for the group of sartans

INN		Romania Number of trademarks	Bulgaria Number of trademarks	Overlapping trademarks	Romania Reimbursed percentage	Bulgaria Reimbursed percentage
Losartan	50 mg	8	6	3	90%	25%
	100 mg	6	2	2	90%	25%
Valsartan	40 mg	3	-	-	50%	-
	80 mg	11	1	-	50%	25%
	160 mg	12	12	6	50%	25%
	320 mg	-	1	-	-	25%
Irbesartan	75 mg	3	-	-	50%	-
	150 mg	15	5	1	50%	25%
	300 mg	14	6	-	50%	25%
Candesartan	8 mg	14	6	2	50%	25%
	16 mg	14	5	2	50%	25%
	32 mg	11	5	2	50%	25%
Telmisartan	40 mg	13	2	2	50%	25%
	80 mg	13	10	5	50%	25%

Reimbursed diuretics are more in Romania. There are 18 products with the INN indapamide 1.5 mg in Romania compared to 12 in Bulgaria, and 7 products of furosemide 40 mg, compared to 1 in

Bulgaria. Torasemide is not reimbursed in RO, but in BG it is included in the PDL (Table VI). Indapamide 1.5 mg has a higher average price in Romania in comparison to Bulgaria ($p > 0.05$).

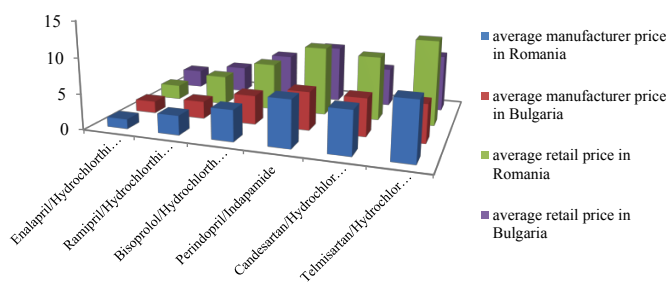


Figure 6.

The comparison of average prices in Romania and Bulgaria for the fixed doses combinations

Table VI

Trademarks per dosage form and reimbursed percentage per INNs for the group of diuretics

INN		Romania Number of trademarks	Bulgaria Number of trademarks	Overlapping trademarks	Romania Reimbursed percentage	Bulgaria Reimbursed percentage
Hydrochlorothiazide	25 mg	1	3	-	90%	25%
Indapamide	1.5	18	12	7	90%	25%
	2.5	3	3	-	90%	25%
Torasemide	5 mg	-	3	-	-	50%
	10 mg	-	3	-	-	50%
Furosemide	40 mg	7	1	-	90%	50%

In Romania, most of the observed medicines have been included in Sublist A and they are 90% reimbursed by the National Health Fund. 50% reimbursement rates for lercanidipin, sartans, and FDCs in RO. In Bulgaria, CV medicines are reimbursed at a rate of 50%, apart from a 25% rate for ACE inhibitors, sartans, indapamide, and hydrochlorothiazide (Table II - VII).

There are differences between the reimbursed fixed dose combinations (FDS) in Bulgaria and Romania. In Bulgaria, there are more FDCs available (Table VII). The average manufacturer and retail prices of FDCs are higher in Romania for most of the products ($p < 0.05$). Fixed dose combinations in both countries are 50% reimbursed (Figure 6).

Table VII

Trademarks per dosage form and reimbursed percentage per INNs for the observed fixed dose combinations

INN		Romania Number of trademarks	Bulgaria Number of trademarks	Overlapping trademarks	Romania Reimbursed percentage	Bulgaria Reimbursed percentage
Enalapril/ Hydrochlorthiazide	10/12.5 mg	2	1	1	90%	50%
	10/25 mg	2	1	1	90%	50%
	20/12.5 mg	1	4	1	90%	50%
Ramipril/ Hydrochlorthiazide	2.5/12.5 mg	3	3	1	90%	50%
	5/25 mg	3	5	2	90%	50%
	10/25 mg	-	1	-	-	50%
	10/12.5 mg	-	1	-	-	50%
	5/12.5 mg	-	1	-	-	50%
Bisoprolol/ Hydrochlorthiazide	10/6.25 mg	1	1	-	50%	50%
	2.5/6.25 mg	1	1	-	50%	50%
	5/6.25 mg	1	1	-	50%	50%
	10/2.5 mg	-	1	-	-	50%
	5/12.5 mg	-	2	-	-	50%
Perindopril/ Indapamide	2/0.625 mg	4	3	1	50%	50%
	2.5/0.625 mg	2	1	1	50%	50%
	4/1.25 mg	5	4	2	50%	50%
	8/2.5 mg	1	1	1	50%	50%
	10/2.5 mg	1	2	1	50%	50%
	5/1.25 mg	3	2	2	50%	50%
Losartan/ Hydrochlorthiazide	50/12.5 mg	3	5	1	50%	50%
	100/12.5 mg	1	1	-	50%	50%
	100/25 mg	-	1	-	50%	50%
Valsartan/ Hydrochlorthiazide	160/12.5 mg	1	9	-	50%	50%
	160/25 mg	1	11	-	50%	50%
	320/12.5 mg	1	1	-	50%	50%
	320/25 mg	1	1	-	50%	50%
	80/12.5 mg	1	2	-	50%	50%
Irbesartan/ Hydrochlorthiazide	150/12.5 mg	8	3	-	50%	50%
	300/12.5 mg	8	4	-	50%	50%
	300/25 mg	5	-	-	50%	50%
Candesartan/ Hydrochlorthiazide	16/12.5 mg	7	6	2	50%	50%
	8/12.5 mg	7	4	1	50%	50%
	32/12.5 mg	-	2	-	50%	50%
	32/25 mg	-	1	-	-	50%
Telmisartan/ Hydrochlorthiazide	80/12.5 mg	8	11	5	50%	50%
	80/25 mg	7	8	4	50%	50%

The average manufacturers prices for all products under the same INN differs statistically significant ($p = 0.00057$), as well as the average retail prices ($p = 0.000128$). T-test analysis shows that there are statistically significant differences in almost all prices of CV medicines between the two countries ($p < 0.05$) thus rejecting the null hypothesis (Table VIII).

The research confirms that various factors are influencing the prices [22]. They could be from the methodology itself, reimbursement policy, etc. Both countries under consideration use the international reference pricing system, setting the lowest price as the main reference price. The differences are in the number of reference countries, margins and regressive scale levels. 9 of all reference countries are overlapping. The referent countries, margins, VAT, and methodology of price formation can lead to uncertainty and cascade

effects on prices of prescription medicines, due to the unintended consequences of factors such as exchange rate, number of products per INN, and price revision.

In general, manufacturers' and retail prices are slightly lower in Bulgaria. The differences are statistically significant for most of the compared INNs. Manufacturers' prices of 5 out of 24 INNs did not differ statistically significant. The latter is also valid for 4 retail prices.

The lower margins for wholesale and retail pharmacy in Bulgaria lead to a lower retail price, regardless of the higher VAT (20% compared to 9% in Romania). The comparison of average prices at pharmacy level reveals statistically significant differences, too. The VAT influence is not so significant as that of the margins in formation of the final pharmacy price.

Higher margin and low VAT can equalize prices to those calculated at lower margins and higher VAT. We found that in Romania one INN has numerous generic alternatives, and that the average prices are higher in comparison to Bulgaria. Generic competition influences the prices of products within a country but it does not significantly affect drug prices at an international level (between countries). Differences

at national level largely influence the price differences [17, 23]. Bulgaria and Romania follow the same methodology, but the differences in VAT and margins set different retail prices, reflecting on the pharmaceutical industry. On the other hand, differences in reimbursement percentage define patient co-payment and affect patients' access to medicines, as well as affordability.

Table VIII

Average (SD) manufacturer and retail prices per INN

INN	Romania Manufacturer price (euro)	Bulgaria Manufacturer price (euro)	p value	Romania Retail price (euro)	Bulgaria Retail price (euro)	p value
Amlodipine	2.07 (1.14)	1.4 (0.99)	p < 0.05	3.06 (1.85)	2.13 (1.5)	p < 0.05
Felodipine	4.4 (1.73)	4.37 (1.74)	p > 0.05	8.81 (4.91)	6.59 (2.55)	p < 0.05
Verapamil	2.68 (0.5)	2.61 (0.48)	p > 0.05	4.13 (0.77)	3.98 (0.72)	p > 0.05
Lercanidipine	4.17 (1.65)	4.07 (1.62)	p > 0.05	6.31 (2.42)	6.15 (2.39)	p > 0.05
Lisinopril	1.95 (0.98)	1.77 (0.8)	p < 0.05	3 (1.52)	2.71 (1.34)	p < 0.05
Ramipril	1.96 (0.96)	1.83 (0.7)	p < 0.05	3.03 (1.48)	2.79 (1.07)	p < 0.05
Quinapril	2.17 (0.54)	2.15 (0.55)	p > 0.05	3.34 (0.84)	3.28 (0.83)	p > 0.05
Fosinopril	3.76 (0.83)	3.05 (0.91)	p < 0.05	5.8 (1.29)	4.65 (1.38)	p < 0.05
Perindopril	6.1 (2.58)	4.49 (2.33)	p < 0.05	9.1 (3.65)	6.77 (3.43)	p < 0.05
Bisoprolol	1.85 (0.89)	1.85 (0.75)	p > 0.05	2.85 (1.38)	2.81 (1.15)	p > 0.05
Carvedilol	2.81 (1.5)	3.3 (2.22)	p < 0.05	4.29 (2.26)	4.98 (3.29)	p < 0.05
Nebivolol	4.15 (1.12)	3.01 (0.65)	p < 0.05	6.3 (1.56)	4.59 (0.99)	p < 0.05
Losartan	3.61 (1.98)	2.99 (1.31)	p < 0.05	5.5 (2.96)	4.56 (2)	p < 0.05
Valsartan	7.14 (6.00)	4.76 (1.46)	p < 0.05	10.6 (8.27)	7.21 (2.13)	p < 0.05
Irbesartan	8.64 (3.37)	6.66 (2.80)	p < 0.05	12.57 (4.61)	9.92 (4.15)	p < 0.05
Telmisartan	7.47 (1.81)	4.61 (1.30)	p < 0.05	11.17 (2.64)	6.96 (1.90)	p < 0.05
Candesartan	9.5 (2.75)	7.3 (2.43)	p < 0.05	13.77 (3.68)	10.87 (3.61)	p < 0.05
Indapamide	1.99 (0.59)	1.68 (0.44)	p < 0.05	3.07 (0.92)	2.56 (0.67)	p < 0.05
Enalapril/Hydrochlorthiazid	1.35 (0.14)	1.69 (0.58)	p < 0.05	2.09 (0.22)	2.58 (0.88)	p < 0.05
Ramipril/Hydrochlorthiazid	2.7 (0.59)	2.45 (0.56)	p < 0.05	4.16 (0.90)	3.74 (0.85)	p < 0.05
Bisoprolol/Hydrochlorthiazid	4.33 (0.28)	4.07 (0.16)	p < 0.05	6.67 (0.43)	6.2 (0.25)	p < 0.05
Perindopril/Indapamid	6.53 (3.55)	5.39 (2.80)	p < 0.05	9.71 (4.99)	8.1 (4.12)	p < 0.05
Candesartan/Hydrochlorthiazid	6.01 (2.17)	5.3 (1.51)	p < 0.05	9.03 (3.13)	5.47 (4.02)	p < 0.05
Telmisartan/Hydrochlorthiazid	8.09 (4.32)	5.33 (1.31)	p < 0.05	11.89 (5.9)	8.04 (1.9)	p < 0.05

Conclusions

Overall, this study reveals that despite simultaneously joining the European Union and following the same European regulations, the fact that the decision on what approach to take for price formation is left to the national policy leads to differences in patient co-payment, manufacturer and retail prices, which in turn influences both the pharmaceutical industry and patients' access to medicines.

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