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IMPACT OF THE GENERIC COMPETITION ON USAGE AND PRICES OF CARDIOVASCULAR MEDICINES ON THE BULGARIAN PHARMACEUTICAL MARKET

Abstract:

Background

During the last decades a tremendous progress was made in the discovery and development of lot of new molecules in the medicine area. These new molecules are at the origin of new pharmaceutical products, called the "originator products", which are patent protected for the inventor during a period of 15 to 20 years. After this period, these products can be copied by competitors, giving what we called "generics products". Simultaneously after the first original products started to be developed chemically similar products called "me too" drugs that could be considered as therapeutic competitors of the first medicine.

Main objective

This research focuses on the effects of the arrival of generics and/or therapeutic competitors on the market, in terms of impacts on the market share and prices.

Methodology

We follow between 2005 and 2008 three families in the cardiovascular area: the family of inhibitors of Angiotensin - Converting Enzyme (called "ACE inhibitors"), the family of Sartans and the family of Statins. They have been studied on the Bulgarian market due to the fact that there is no legal regulation in this country stimulating the development of the generic market. The official database of the Bulgarian Health Insurance Fund was used to test our two hypothesis concerning the introduction of generics and their impact on market share and prices. To test our hypothesis a t-test analysis, Kolmogorv Smirnov, one and two – way ANOVA analyses were performed.

Results

Our results confirm that of similar studies that the generic competition, in general, changes the market. These changes benefit to the generic products and decrease the medicines prices.

The generic competition is not regulatory supported in the country and this fact could influence negatively our study because it does not correspond to the world tendencies.

Further more our results confirm some other publications that the creation of sustainable generic pharmaceutical market requires active regulatory and marketing measures at all levels including incentives for manufactures, physicians and dispensers. It is not sufficient only to shorten the marketing authorisation process for generic medicines at European level but every country should perform its own measures. If the government wants to benefit from the generic drug policy and thus to reduce the medicines prices in the country, it should create a generic medicines policy affecting all the participants in the pharmaceutical sector in the country.

Key words:

pharmaceutical market – generics – competitors - market share - prices

Introduction

During the last three decades a tremendous progress has been made in the discovery and development of lot of new molecules in many pharmaceutical areas. The therapeutic groups of cardiovascular medicines are good example of such a development with the families of inhibitors of Angiotensin-Converting Enzyme ("ACE inhibitors"), sartans and statins [1, 2].

Besides these new families of real innovative treatment which use some new molecules and brought some new products (what we call "originator"), these ones have been copied by competitors after 15 or 20 years of patent. These last products (what we call "generics") have the same chemical structure and have been proven to be essentially similar [3].

To give an example, a new molecule, the ramipril, in the family of ACE has been launched by the pharmaceutical laboratory SANOFI AVENTIS under the name of Triatec®. When the patent of this product has expired, a competitor, the pharmaceutical laboratory QUALIMED launched the same product in terms of molecule and effects, so, a generic, called Ramipril Qualimed®. Within the same therapeutic group already MSD did launch enalapril as Renitec® that is a "therapeutic competitor" possessing small variation in the chemical structure. Following the same approach of modification of the first molecule later the perindopril, trandalopril, fosinopril and s.o were added the ACE inhibitors and thus the whole therapeutic family started to expand.

Conceptual framework and Literature review

The generics create competition and drive medicines prices down [4]. Many studies show in fact that when a new medicinal product (a new molecule giving an originator or the same molecule giving a generic) appears on the pharmaceutical market, it affects the market pattern and prices of the existing generic and/or therapeutic competitors [5]. To what extend and for how long time it happens depends on the specific characteristics of the national market, the laws concerning the generics and the pharmaceutical companies' policy. A common perception is that the original medicinal product, ensure new therapeutic options for severe

diseases, while the generic medicines support the sustainability of healthcare provision and contribute to maintain a control over the pharmaceutical expenditures [6, 7].

Some countries use laws to promote the prescription and the delivery of generics to decrease the health expenditures. Studies focusing on the market policy of the pharmaceutical manufacturers consider that every new product within the same therapeutic class is characterised by simultaneous entry by competitors rather than sequential [8]. It means that the expiry of a product patent is accompanied by the entry at the same time, sometimes the same day, by different generics. Models have been created to calculate the aggregated demand and supply features influencing the generic medicines market [9].

During the last two decades a reference pricing approach was developed and started to be used in a lot of European countries[10]. The reference prices are established after an international or national comparison of the prices of the generic or therapeutic alternatives [11]. The reference price could be either the low or the average price within the compared group of products [12]. This policy stimulates researches in the area of price comparison and analysis of the factors influencing price changes as are the generic policy and competition.

The cardiovascular medicines are of a particular interest for studying the competition between originators and generics. They have the role of leader on the global medicine market with more or less 10% of the market sales in value [13]. For this reason this class presents a big interest for the pharmaceutical laboratories and we can find some new innovative products and some generics. This interest is also shared by the Health Authorities, which want to control the increasing expenditures, analysing their prescription and their usage and creating national rules for price control.

In this category of treatment, three groups of therapeutics are more interesting due to the presence of innovative molecules and the arrival of generics: the families of inhibitors of Angiotensin-Converting Enzyme ("ACE inhibitors"), sartans and statins [14,15,16,17].

The ACE inhibitors appeared with the discovery of the captopril molecule in 1975 that was considered as a breakthrough due to its novel mechanism of action and the revolutionary development process. Nowadays this therapeutic group includes 16 differents molecules with a similar structure at the origin of more than a thousand of products combining the originators and their generics. Only 2 molecules are still under patent protection.

The Sartans (also named "Angiotensin Receptor Blockers" or "Angiotensin II Receptor Antagonists") modulate the rennin-angiotensin-aldosterone system and thus decreased the blood pressure. The tetrazole group is a main part of the chemical structure of Losartan, Irbesartan, Olmesartan, Candesartan and Valsartan. In addition, Losartan, Irbesartan, Olmesartan, Candesartan and Telmisartan include one or two imidazole groups [12, 13]. Within the group of sartans, Valsartan and Losartan have expired patents and generics available on the market.

The Statins are lipid lowering agents which appeared in 1979 with the Lovastatin and closely after the Simvastatin. The statins therapeutic group is composed of 6 molecules from which 3 have expired patent.

Main objective

The aim of this study is to analyse the changes in the drug usage and prices in these three pharmaco-therapeutic groups acting on cardiovascular system on the Bulgarian market between the years 2005-207.

Hypothesis tested

Due to the fact that there is no law regulation on the generic medicines in Bulgaria, we want to test two hypotheses:

Hypothesis 1: The introduction of new medicinal products (originators or generics) affects the sales data and/or market share within the group.

Hypothesis 2: The introduction of new medicinal products (originators or generics) decreases the prices of the competitors within the group.

Methods

We collect information for the prescription of 20 different products in the cardiovascular classes of medicines: 9 ACE inhibitors, 5 Sartans and 6 Statins, authorized for sale on the Bulgarian market in 2005-2007, using the official database of the Health insurance fund.

It was created a database for the prescribed packaging of 74 different dosage forms of medicinal products sold under the observed 20 International Nonproprietary Names (INN). To summarise the differences among the packaging the usage was recalculated in milligrams for every INN during the particular observed years.

The information for the drug prices was gathered from the official register of the Ministry of Health for all authorised trade names of observed medicines [18]. Then, the prices were recalculated per milligram for every dosage form and within the group of products under the same INN. To calculate the mean price per INN and per mg a descriptive statistic was applied.

To test the first Hypothesis we first apply the Kolmogorv Smirnov (K-S) test towards the sales data during the observed years. The K-S test seeks differences between the distribution function of sales data in 2006 in comparison with 2005 and 2007 in comparison with 2006. The test provides information for the differences between the observed years by rejecting the null hypothesis if no differences exist.

Then to analyse the possible differences among the sales of particular INNs during the observed years we recalculate the market share of every INN out of all sold milligrams of INNs within every therapeutic group. The results are in the Figure 1 for the therapeutic group of ACE Inhibitors, Figure 2 for the therapeutic group of ACE Sartans and Figure 3 for the therapeutic group of Statins. We then compare in a second step the proportions using the z-test analysis for every INN assuming 95% CI for the changes in proportions of INN, comparing the data for the year 2005 versus the year 2006 and the year 2006 versus the year 2007. The z-test provides information for the statistically significant differences among the proportions of INNs sold during the years 2005, 2006 and 2007.

To test the second Hypothesis, we first perform two-way ANOVA analyses to evaluate the differences of prices in mg of active substances during the observed years for the therapeutic groups. If there was a difference established we next perform a one way ANOVA analysis to evaluate them per INNs and among the therapeutic alternatives. In the group of Sartans, no generic competitors were available for any of the 5 observed INNs and one way ANOVA analysis was applied only for the alternatives within the therapeutic group.

Results

Out of all collected medicinal products in the therapeutic class of ACE Inhibitors, we found only 2 INN with generics: the enalapril and the lisinopril. In the therapeutic class of Statins we found also 2 INN with generics: the simvastatin and the lovastatin. In the last therapeutic class studied, the Sartans, we found 1 INN with generic, the losartan. The others INN within these three therapeutic groups are considered as therapeutic competitors. All these results are in the Appendix 1.

In the product class of ACE Inhibitors, the enalapril in milligrams is the leader of the class with 93,1 % of the market share in 2005 when we begin our study. It's not possible to see it in this appendix but the enalapril permanently increased it's market share previously. It market share decreased in 2006 (88,6 %) and 2007 (86,34 %).

All products within the group, except the quinapril (which decrease in 2007 versus 2006) perform steady increase in their usage measured in milligrams of active substance sold (Appendix 1).

We can say that the faster growing of the therapeutic group and introduction of different new molecules within the class leads to the decrease in the market share of enalapril during 2006 and 2007 with 4 % every year (Figure 1). On the opposite, the market share of the therapeutic competitors slowly and permanently increases every year thus taking part of the enalapril market share.

It is also necessary to point out that after the introduction of the generic competitor to lisinopril in 2006, its market share increase with a bigger percentage (from 2,34 % in 2005 to 3,65 % in 2006) than the share of the others therapeutic competitors within the group.

Placed Here - Figure 1: Relative Market Share of ACE Inhibitors sales during 2005, 2006 and 2007.

In the product class of Sartans, the biggest market share in 2005 was that of telmisartan, probably because of the promotional price of the originator. In the second year with the introduction of losartan generics and significant reduction in its price, the market share of losartan increases almost 6 times thus taking a leading position in the group.

The market dynamic in proportions of INN sold within the group of Sartans is mostly evident in comparison with the previous group.

Placed here - Figure 2: Relative Market Share of Sartans sales during 2005, 2006 and 2007.

In the product class of Statins, we found an increase of usage in milligrams of all products and especially those INN which have a generic version (lovastatin and atorvastatin). The lovastatin increases its' usage 2 fold time in 2007 in comparison with 2005 as seen in the Appendix 1. In this group, we observed that after the increase of the number of generic competitors under the same INN, the relative market share of the INN increases as it's the case for simvastatin. We can consider that the introduction of new generics did not deprive the sales data of the originator immediately but in general contribute to the accumulation in market share of the belonging INN.

Placed here - Figure 3: Relative Market Share of Statins sales during 2005, 2006 and 2007.

After applying the Kolmogorov Smirnov test we observed that there is a statistically significant difference among the sales data during 2006 and 2005 as well as during 2007 and 2006 (Table 1). It confirms that the sales data of the observed therapeutic groups changes statistically significantly during the analysed years.

Placed here – Table 1: Results of the Kolmogorov Smirnov test

To test the differences among the INNs sales data the z-test analysis was applied. The results of the z-test analysis confirm that almost for all the products, except for the perindopril and trandalopril in the class of ACE inhibitors and irbesartan from class of Sartans, the changes in the market share are statistically significant (Table 2). For all of these three products there is no generic competitor. So we can conclude that the introduction of generics changes the sales data of the INNs and contribute to the changes in the sales data of the therapeutic groups.

Placed here – Table 2. Results of the z-test analysis

Concerning the prices, all of them decreased during the observed period from 2005 to 2007 but it was mainly due to the changes in the regulation (Appendix 1) [18]. The changes affect mainly the decrease of the distributors margins (wholesale and retail) almost half for the medicines paid by the health insurance fund**.**

For the group of ACE inhibitors the two way ANOVA analysis confirms that the prices in mg differ among the observed products ($p<0.05$) but did not differ statistically significant during the years for the whole group ($p>0.05$). Multiple comparison among the prices of different INNs establish statistically significant differences ($p < 0.05$) among the prices in mg between trandalopril and all other INN within the group (benazepril; cilazapril; enalapril; fosinopril; lisinopril; perindopril; quinapril and ramipril). The one way ANOVA analysis revealed significant differences ($p < 0.05$) in the prices during the years only for lisinopril (Table 3).

The Statines group include 5 INN with 20 to 31 dosage forms per year. In this group we also did not found significant prices changes among the years ($p>0.05$), but prices of the INNs within the group differs ($p<0.05$). By applying multiple comparison the difference among lovastatin and rosuvastatin was evaluate as statistically significant. No differences among the prices for particular INNs were observed (Table 3).

For the group of Sartans we also found through the two way ANOVA analysis that the prices in mg differ among the observed products ($p<0.05$) but did not differ significantly during the observed years for the whole group ($p>0.05$). Multiple comparisons among the INNs within

the therapeutic groups revealed significant prices differences among telmisartan and eprosartan. No differences among the prices for particular INNs were evaluated separately (Table 3).

The results from two way and one way ANOVA analysis revealed that there are no statistically significant changes in the prices of the observed INN, except for lisinopril, but there are significant prices differences among the therapeutic competitors within the groups.

Thus our second Hypothesis is not fully confirmed.

Discussion, limitations and further research

The cardiovascular medicines market characteristics are of importance for the national markets because of lots of reasons as are their permanent growing usage, progress in new molecules discovery, changes in life expectancy of the population, creation of the national rules for prices control and cost containment measures.

We do observe a dynamic national market of cardiovascular medicines that correspond to the word tendencies but the competition is mostly evident at the therapeutic groups level than at the generic ones [14].

Our results confirm as similar studies that the generic competition, in general, changes the market. These changes benefit to the generic products and decrease the medicines prices.

The generic competition is not regulatory supported in the country and this fact could influence negatively our study because it does not correspond to the world tendencies [17].

Further more our results confirm some other publications that the creation of sustainable generic pharmaceutical market requires active regulatory and marketing measures at all levels including incentives for manufactures, physicians and dispensers [18, 19]. It is not sufficient only to shorten the marketing authorisation process for generic medicines at European level but every country should perform its own measures [20].

Our study possesses some limitations as the fact that we compare the mean prices per milligram and not per Defined Daily Dose (DDD) that is more therapeutically compatible. Instead of the fact that DDD is established in milligrams for most of the medicines we

consider that similar analysis should be done for the changes in prices per DDD because it is most compatible with the therapeutic reasoning.

The fact that we could not establish strong evidences supporting our second hypothesis could be explained with the short period of observation and slow entrance of generic medicines in the positive drug list.

Generic competitors were found only for 5 out of 20 compared INN and for 2 of them only one competitor existed that limits the evaluation of the impact of generic competition on prices. We didn't analyse the way of the communication from the pharmaceutical laboratories towards the prescribers, which can have an effect.

Further studies should be organised to evaluate the changes in prices during a longer period and when more generic competitors will be available in the country. The national generic medicines policy is also of importance to increase the medicines prices competition.

Conclusion

There are two main conclusions from our study. The first one is that for the therapeutic groups which include lot of similar molecules it is important to consider the competition among the molecules and not only the generic entrance. Originating pharmaceutical companies seems to compete among them selves at therapeutic level and with generic companies at price level.

The second conclusion is that the introduction of generic medicines did not affect immediately the mean market prices and needs more than 3 years of stronger competition to benefit the market.

From the managerial point of view it is necessary to point out that if the government wants to benefits from the generic drug policy and thus to reduce the medicines prices in the country, it should create a stronger supporting environment affecting all the participants in the pharmaceutical sector in the country.

Bibliography

[1] Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. *J Intern Med.* 2008 Sep; 264 (3): 224-36.

[2] Raizada MK, Ferreira AJ. ACE2: a new target for cardiovascular disease therapeutics. *J Cardiovasc Pharmacol.* 2007 Aug; 50 (2):112-9.

[3] Morgan Steven G,Kenneth L Bassett,James M Wright,Robert G Evans,Morris L Barer, Patricia A Caetano,Charlyn D Black "Breakthrough "drugs and growth in expenditure on prescription drugs in Canada, *BMJ* 2005; 331 (8): 815-16

[4] Lee TH. "Me-too" products -- friend or foe? *N Engl J Med* 2004;350:211-212

[5] Dirach J., New safe medicines faster: A new concept for drug development. *EUFEPS.* 27 Feb; 1-5

[6] Fiona M. Scott Morton, Entry Decisions in the Generic Pharmaceutical Industry, in: *NBER (National Bureau of Economic Research) Working Paper serie*s, No. 6190, Cambridge, 1997, p. 8.

[7] Fox P.D., Prescription Drug Benefits: Cost Management Issues for Medicare. *Health care financing review*, Winter 2003-2004 (25); 2: 7-21

[8] Fiona M. Scott Morton, "Entry Decisions in the Generic Pharmaceutical Industry", in: NBER (National *Bureau of Economic Research) Working Paper serie*s, No. 6190, Cambridge, 1997, p. 8.

[9] Gascon F., D. de la Fuente, J. Puente, J. Lozano. On macroeconomic characteristics of pharmaceutical generics and the potential for manufacturing and consumption under fuzzy conditions. *Artificial Intell in medicines* 2007; 41: 223-235

[10] Huttin C. Experiences with reference pricing. *Int J Risk Saf Med* 2002; 15: 85-91

[11] Mestre - Ferrandiz J. , Reference prices and generic medicines: What can we expect?*, Journal of Generic Medicines*, 2003; 1: 31–38

[12] Mrazek MF. Comparative approaches to pharmaceutical price regulation in the European Union. *Croat Med J* 2002; 43 (4): 453-61

[13] Words Health Organisation. The world medicines situation. WHO, Geneva, 2007

[14] http://www.drugs.com. (Assessed March 2008)

[15] Luno J, Praga M, de Vinuesa SG. The reno-protective effect of the dual blockade of the renin angiotensin system (RAS). *Curr Pharm Des* 2005;11(10):1291-300

[16] Rossi S et al. Australian Medicines Handbook 2006. Adelaide; 2006.

[17] Levy BI. How to explain the differences between renin angiotensin system modulators. *Am. J. Hypertens. 2005; 18: 134S–141S*

[18] Ministry of health. Drug price registry. www.mh.government.bg (Assessed 2005, 2006, and 2007)

[19] National Peoples Assembly. Law on Medicinal products for human medicine. *Gov. Newspaper,* April 2007

[20] Simoens S., S. de Coster. Sustainable generic medicines market in Europe. Research center for pharmaceutical care and pharmacoeconomics. Kotholieke Universitet, Leuven, 2006

[21] NERA (National Economic research Associate). Policy Relating to Generic Medicines in the OECD. http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/nerareport.pdf (Assesed August 2009)

[22] Adriaen M., Kristof De Witte, S. Simoens. Pricing strategies of originator and generic medicines following patent expiry in Belgium. *Journal of Generic Medicines* 2008; 5: 175–187

[23] EU. Directive 2001/83 of the European parliament and of the council of 6 November 2001 and on the community code relating to medicinal products for human use. *Official Journal* L–311,28/11/2004, p. 67 – 128

Figure 1: Relative Market Share of ACE Inhibitors sales during 2005, 2006 and 2007.
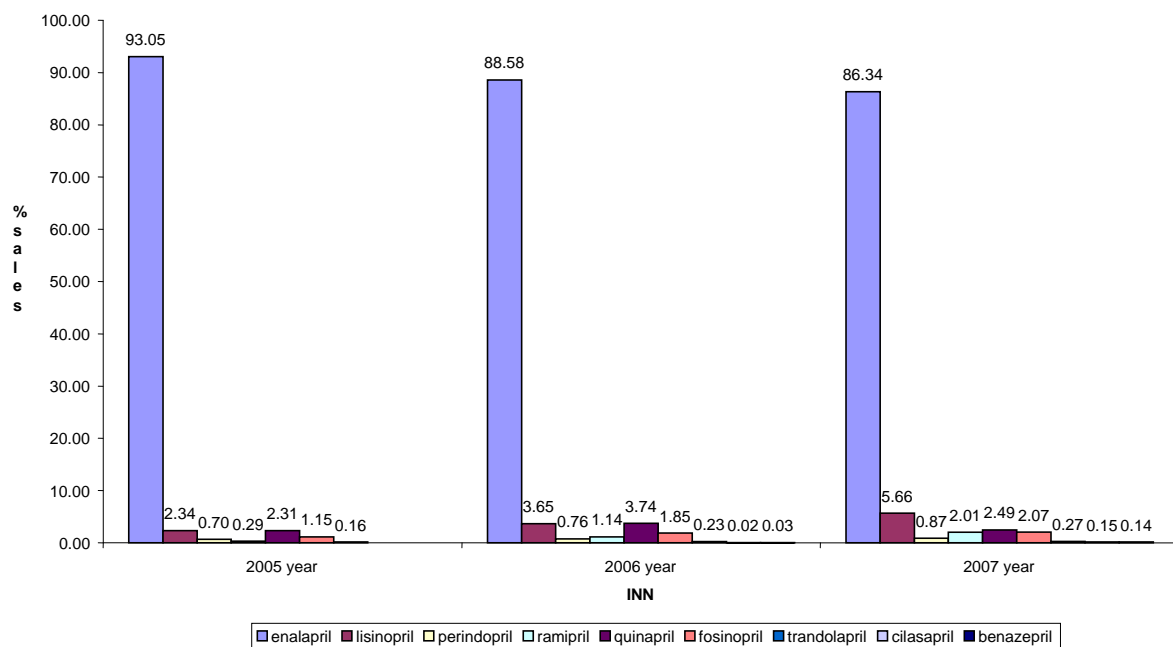
Figure 2: Relative Market Share of Sartans sales during 2005, 2006 and 2007.
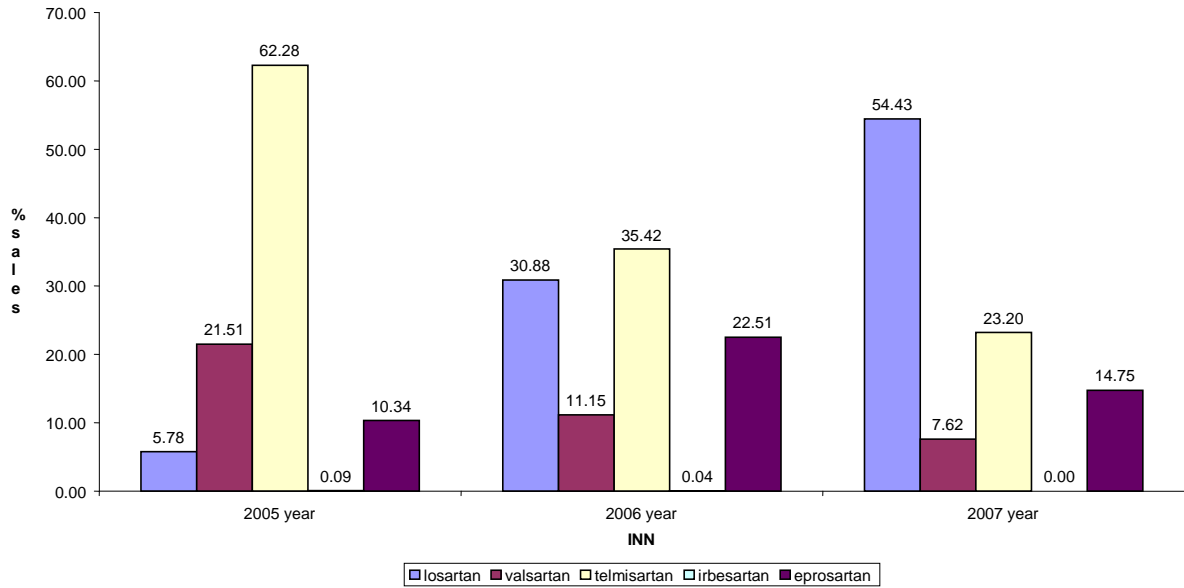
Figure 3: Relative Market Share of Statins sales during 2005, 2006 and 2007.
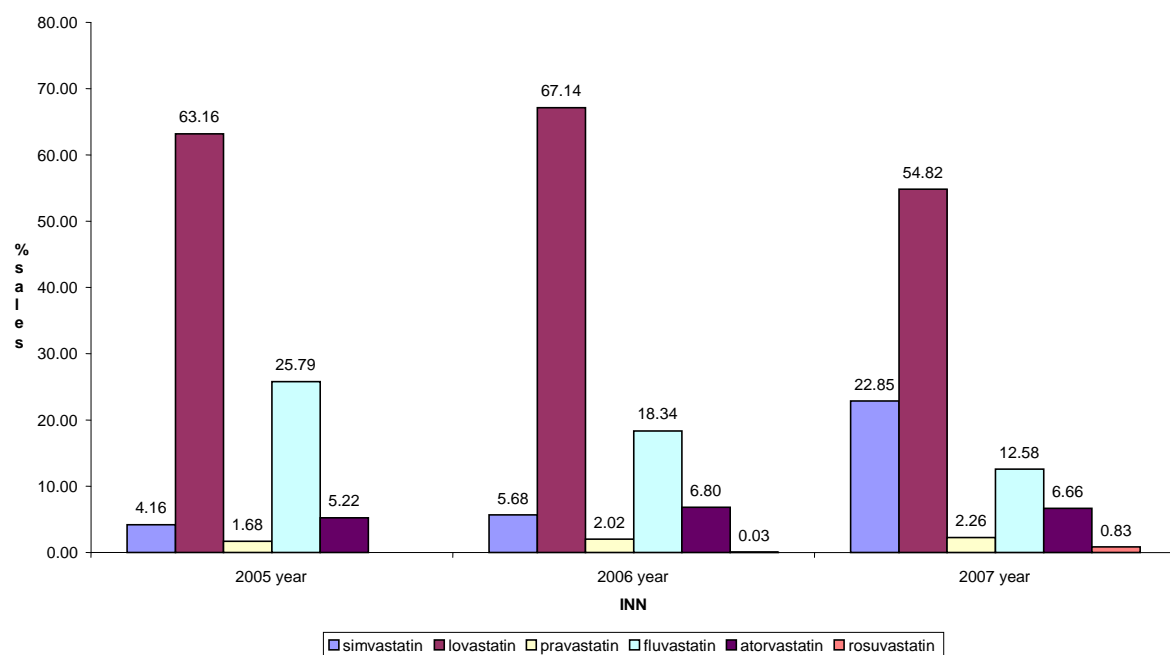
Table 1: Results of the Kolmogorov Smirnov test

INN	Sales data 2005	Sales data 2006	Sales data 2007	K-S 2006/2005	K-S 2007/2006
enalapril	1906795530	2287185280	2362110040		
lisinopril	47860510	94173850	154909420		
perindopril	14378880	19729440	23778840		
ramipril	5880420	29455406	55117400		
quinapril	47253900	96471300	68185500		
fosinopril	23618840	47761840	56553000		
trandolapril	3322444	6061288	7445446		
cilasapril		553630	3979220	Null hypothesis rejected	Null hypothesis rejected
benazepril		692160	3899840		
INN	Sales data 2005	Sales data 2006	Sales data 2007	K-S 2006/2005	K-S 2007/2006
simvastatin	13140540	26303860	125098060		
lovastatin	199510800	310969800	300126000		
pravastatin	5301900	9335100	12384300		
fluvastatin	81453120	84938560	68862080	Null hypothesis rejected	Null hypothesis rejected
atorvastatin	16486500	31483800	36445200		
rosuvastatin		157360	4523400		
INN	Sales data 2005	Sales data 2006	Sales data 2007	K-S 2006/2005	K-S 2007/2006
losartan	15715000	196378000	485893800		
valsartan	58464000	70936320	68051200		
telmisartan	169261120	225245440	207121600	Null hypothesis rejected	Null hypothesis rejected
irbesartan	231000	252000	0		
eprosartan	28089600	143152800	131695200		

Table 2: Results of the z-test analysis

INN	% sales 2005	% sales 2006	% sales 2007	z-test value 2006/2005	Stat sign difference	z-test value 2007/2006	Stat sign difference
enalapril	93.05	88.58	86.34	141.26	Yes	97.70	Yes
lisinopril	2.34	3.65	5.66	14.10	Yes	22.32	Yes
perindopril	0.70	0.76	0.87	0.99	No	1.08	No
ramipril	0.29	1.14	2.01	181.01	Yes	306.23	Yes
quinapril	2.31	3.74	2.49	14.07	Yes	13.61	Yes
fosinopril	1.15	1.85	2.07	217.26	Yes	72.54	Yes
trandolapril	0.16	0.23	0.27	-0.01	No	36.23	Yes
cilasapril		0.02	0.15			16.09	Yes
benazepril		0.03	0.14			17.83	Yes

INN	% sales 2005	% sales 2006	% sales 2007	z-test value 2006/2005	Stat sign difference	z-test value 2007/2006	Stat sign difference
simvastatin	4.16	5.68	22.85	6.30	Yes	105.43	Yes
lovastatin	63.16	67.14	54.82	29.32	Yes	96.19	Yes
pravastatin	1.68	2.02	2.26	40.50	Yes	99.91	Yes
fluvastatin	25.79	18.34	12.58	1247.00	Yes	846.22	Yes
atorvastatin	5.22	6.80	6.66	217.43	Yes	16.39	Yes
rosuvastatin		0.03	0.83			31.085	Yes

INN	% sales 2005	% sales 2006	% sales 2007	z-test value 2006/2005	Stat sign difference	z-test value 2007/2006	Stat sign difference
losartan	5.78	30.88	54.43	2115.57	Yes	5447.45	Yes
valsartan	21.51	11.15	7.62	1699.95	Yes	688.75	Yes
telmisartan	62.28	35.42	23.20	5320.95	Yes	3823.96	Yes
irbesartan	0.09	0.04		-0.05	No		
eprosartan	10.34	22.51	14.75	1550.23	Yes	1683.29	Yes

Table 3: Differences among INN prices during the years (one way ANOVA analysis)

INN	2005			2006			2007			One-way ANOVA
	N dosage forms	Mean price mg	SD	N dosage forms	Mean price mg	SD	N dosage forms	Mean price mg	SD	
enalapril	33	0.0188	0.012688	42	0.017	0.011871	39	0.0192	0.021205	$p > 0.05$
lisinopril	15	0.0427	0.015337	18	0.0389	0.013672	15	0.0192	0.021205	$p < 0.05$
perindopril	2	0.165	0.007071	2	0.16	0	2	0.15	0.014142	$p > 0.05$
ramipril	2	0.1	0	3	0.1233	0.068069	3	0.0833	0.028868	$p > 0.05$
quinapril	2	0.035	0.00707	2	0.185	0.205061	2	0.035	0.007071	$p > 0.05$
fosinopril	2	0.035	0.007071	2	0.035	0.007071	2	0.03	0.014142	$p > 0.05$
trandolapril	2	0.925	0.841457	2	0.64	0.579828	2	0.62	0.579828	$p > 0.05$
cilasapril				1	0.22	0.070711	1	0.18	0.070711	$p > 0.05$
benazepril				1	0.04	.	1	0.05		$p > 0.05$
INN	N dosage forms	Mean Price mg	SD	N dosage forms	Mean price mg	SD	N dosage forms	Mean price mg	SD	
simvastatin	6	0.12	0.093595	6	0.12	0.093595	10	0.035	0.010801	$p > 0.05$
lovastatin	4	0.0125	0.005	4	0.0125	0.005	4	0.01	0.01	$p > 0.05$
pravastatin	4	0.0775	0.062383	4	0.0775	0.062383	2	0.03	0.014142	$p > 0.05$
fluvastatin	1	0.03	.	1	0.03	.	1	0.03	.	$p > 0.05$
atorvastatin	5	0.096	0.039115	5	0.096	0.039115	7	0.0657	0.030472	$p > 0.05$
rosuvastatin				5	0.096	0.039115				$p > 0.05$
INN	N dosage forms	Mean Price mg	SD	N dosage forms	Mean price mg	SD	N dosage forms	Mean price mg	SD	
losartan	2			2			2			
valsartan	1			1			1			
telmisartan	1			1			1			
irbesartan	2			2						
eprosartan	1			1			1			
	7	0.0121	0.008335	7	0.0285	0.030872	5	0.0174	0.007335	$p > 0.05$

INN	2005 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2005	SD	2006 sales in mg	% sales	N trade names	N dosage sales	Mean price mg 2006	SD	2007 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2007	SD
enalapril	1906795530	93.1	9	33	0.0188	0.0130	2287185280	88.6	12	42	0.017	0.0118	2362110040	86.34	11	39	0.01923	0.0212
lisinopril	47860510	2.34	5	15	0.0427	0.020	94173850	3.65	6	18	0.03889	0.0137	154909420	5.66	5	15	0.01923	0.0212
perindopril	14378880	0.70	1	2	0.165	0.0011	19729440	0.76	1	2	0.16	0	23778840	0.87	1	2	0.15	0.0141
Ramipril	5880420	0.29	1	2	0.1	0	29455406	1.14	2	3	0.12333	0.0681	55117400	2.01	2	3	0.08333	0.0289
quinapril	47253900	2.31	1	2	0.035	0.0071	96471300	3.74	1	2	0.185	0.2051	68185500	2.49	1	2	0.035	0.0071
fosinopril	23618840	1.15	1	2	0.035	0.0071	47761840	1.85	1	2	0.035	0.0071	56553000	2.07	1	2	0.03	0.0141
trandolapril	3322444	0.16	1	2	0.925	0.8411	6061288	0.23	1	2	0.64	0.5798	7445446	0.27	1	2	0.62	0.5798
cilasapril							553630	0.02	1	1	0.22	0.0707	3979220	0.15	1	1	0.18	0.0707
benazepril							692160	0.03	1	1	0.04	.	3899840	0.14	1	1	0.05	
SUMM	2049110524	100					2582084194	100					2735978706	100				

INN	2005 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2005	SD	2006 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2006	SD	2007 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2007	SD
simvastatin	13140540	4.16	1	6	0.12	0.0936	26303860	5.68	3	12	0.06917	0.0805	125098060	22.85	4	10	0.035	0.0108
lovastatin	199510800	63.2	2	4	0.013	0.005	310969800	67.2	4	7	0.01143	0.0038	300126000	54.82	2	4	0.01	0
pravastatin	5301900	1.68	2	4	0.078	0.0624	9335100	2.02	2	4	0.0925	0.0640	12384300	2.26	1	2	0.03	0.0141
fluvastatin	81453120	25.8	1	1	0.03	.	84938560	18.3	1	1	0.03	.	68862080	12.58	1	1	0.03	.
atorvastatin	16486500	5.22	2	5	0.096	0.0391	31483800	6.80	2	5	0.078	0.0536	36445200	6.66	2	7	0.06571	0.0305
rosuvastatin							157360	0.03	1	2	0.16	0.0283	4523400	0.83	1	2		
SUMM	315892860	100					463188480	100					547439040	100				

INN	2005 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2005	SD	2006 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2006	SD	2007 sales in mg	% sales	N trade names	N dosage forms	Mean price mg 2007	SD
Losartan	15715000	5.78	2	2			196378000	30.9	2	2			485893800	54.43	2	2		
valsartan	58464000	21.5	1	1			70936320	11.2	1	1			68051200	7.62	1	1		
telmisartan	169261120	62.3	1	1			225245440	35.4	1	1			207121600	23.20	1	1		
irbesartan	231000	0.09	1	2			252000	0.04	1	2			0					
eprosartan	28089600	10.3	1	1			143152800	22.5	1	1			131695200	14.75	1	1		
SUMM	**271760720**	**100**			0.012	0.0083	**635964560**	**100**			0.0285	0.0309	**892761800**	**100**			0.0174	0.0073

APPENDIX 1. Sales and prices values for the observed therapeutic groups and INNs of cardiovascular medicines in 2005, 2006, and 2007