

Drugs with the Highest Drug Expenditure in the Republic of Serbia

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SUMMARY

Introduction: The policy concerning drugs represents a concentrated effort to achieve better health outcomes for all, with a particular focus on people's access to and rational use of medications. On the basis of pharmacoeconomic analyses, it is possible to modify established prescribing habits, it is possible to influence the creation of guidelines, development strategy and long-term health care planning.

Aim: The aim of the work was to determine drugs with the highest expenditure in the Republic of Serbia, and to compare the results obtained in three consecutive years 2016, 2017 and 2018. Also, to analyze which are the most expensive medications listed in the National Register of Medications and what is the trend of changing them.

Material and methods: The drug expenditure was monitored using the ATC/DDD methodology. It implies the classification of medications according to the internationally accepted ATC classification of drugs, while DDD, i.e. defined daily dose, is used as a statistical unit for consumption monitoring. The number of DDD/1,000 inhabitants per day provides an insight into how many inhabitants (out of 1,000 of them) used the observed medication and were exposed to its effects during one day.

Results: The trend of expenditure of these medications was growing exponentially from 2016 to 2018. The most expensive medications per box are from group J - anti-infective drugs for systemic use and L - antineoplastics and immunomodulators, but their expendi-

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ture in the Republic of Serbia is very low. The drugs with the highest price per 1 DDD are: enzymes imiglucerase, laronidase and the biological medication basiliximab in all three years, but considering the indications and rare prescribing, the total cost for these drugs is not high. The largest funds in the Republic of Serbia for the mentioned period were spent on drugs such as: acetylsalicylic acid, paracetamol in combinations, trastuzumab, pantoprazole, amlodipine and rosuvastatin. Comparing the spending on L group of drugs in 2017 compared to 2016, there was a significant increase.

Conclusion: The medications with the highest expenditure in the Republic of Serbia are used very little compared to countries with good pharmacotherapy practice. The most expensive drugs are those that are used for special and rare indications, and large amounts of money are not allocated for them as for some cheaper, but more frequently prescribed drugs.

Keywords: Drugs Expenditure, The Most Expensive Drugs, Drugs Price

INTRODUCTION

The World Health Organization (WHO) recommends that all countries formulate and implement a comprehensive national medication policy as a means of improving access to safe, effective, and good quality medications. In this regard, WHO supports member states in the development, implementation and monitoring of national medication policies and plans aimed at ensuring that: appropriate medications are reliably and consistently available in healthcare facilities; medications are prescribed and dispensed appropriately; medications are accessible; affordable to patients, and patients are protected from excessive costs [1].

The price of a drug or that of technology changes over time and is mainly a function of the market. Prices can be measured and evaluated as the price paid to the manufacturer, the price paid by the consumer or patient, or the price paid by the supplier. It is typical that a new medication is launched under patent and may have a high price until the patent expires and competition and/or generic products appear. The prices of generic versions that are registered after the patent expires are usually quickly reduced, often more than 90%. Many countries are unable to take advantage of cheaper generic products due to delays in market entry or lack of effective competition. Flexibilities based on the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement allow countries to gain access to medications that are still under patent in other countries, in the interest of public health [2].

The high prices of many new drugs pose a challenge for health systems and for pa-

tients who have to pay for them out of their own pocket (as is the case in most low- and middle-income countries). The recent approval of high-priced new drugs has fueled a new global debate on drug costs and calls for a fair pricing model for both drug development and medication supply [3].

According to the Regulation on the Criteria for the Formation of Medication Prices in Serbia, the reference countries when determining the maximum prices are Slovenia, Croatia and Italy [4].

Positive drugs lists are the lists formed by health insurance funds with a list of drugs that are prescribed at the expense of insurance funds. Some countries have multiple positive lists (including Croatia, which has a basic and supplementary list), while other countries have a single positive list that is divided into different parts according to the different reimbursement and/or prescribing rules that apply. Positive lists are an important tool for prioritizing drugs for reimbursement according to the principles of the essential medication list [5]. The criteria for putting a medication on the positive list are pharmacotherapeutic or pharmacoeconomic justification [6].

The main reason why the development of pharmacoeconomics was turbulent and intense was the increase in the cost of drugs. In order to better dispose of financial resources, generous analyzes and comparisons of the price and outcome of the application of new, more expensive drugs are needed, with the price and outcome of already existing, standard therapies. In this way, it is possible

to direct available resources on financing the most profitable therapeutic strategies [6].

The most significant causes of the increase in treatment costs are: aging of the population, increasing number of chronic patients, large-scale preventive health programs, introduction of new drugs (biological therapy), expansion of indications for existing drugs, pressure from the pharmaceutical industry, availability of information about drugs [7].

Due to the increase in costs on the one hand, and limited resources on the other, detailed analyses of all health, therapeutic or prophylactic procedures are necessary. In addition to efficiency and safety, it is important to examine profitability. Profitability becomes one of the basic criteria for placing drugs on the positive list.

Effectiveness is a very important link in treatment, and it implies a state where no effective intervention is denied to an individual, taking into account costs and efficiency. The additional costs are examined if it is possible to apply a more expensive newly registered drug instead the standard one [6].

Total sales in the pharmaceutical industry in Serbia, in 2014, amounted to 92.43 billion dinars. However, compared to the region of Central and Eastern Europe, where the average is 231 dollars per capita, pharmaceutical expenditure in Serbia is one of the lowest with 146 dollars per capita on average [8].

The use of drugs includes the circulation, distribution, prescribing and administration of drugs in the community, with an emphasis on medical, social and economic consequences. Monitoring the prescribing and use of drugs significantly contributes to the assessment of pharmacotherapeutic attitudes and prescribing habits in practice and enables the determination of factors that influence excessive or insufficient use of certain drugs [9]. Drug consumption is monitored using the ATC/DDD methodology, which involves classifying drugs according to the internationally accepted ATC classification of drugs and using the defined daily dose (DDD) as a statistical unit for monitoring drug expenditure.

The ATC system is a classification system that divides drugs into groups based on the organs or systems they affect in accordance with their chemical, pharmacological and therapeutic properties. Each substance is identified by a specific alphanumeric code, so

it is possible to group those with similar characteristics into ATC levels [10].

In order to enable the comparison of the intensity of use of certain pharmacotherapeutic groups of medications over time and various countries, a special statistical unit for monitoring the use of drugs, or defined daily dose (DDD), was created. This unit is independent of price, trademark, package size and even pharmaceutical form. The concept with defined daily doses (DDD) as a statistical unit of use represents an agreed amount of drug, which is most often used for the most common indication. However, it is important to keep in mind that DDD is a statistical and not a recommended unit, and that it reflects the most commonly used dose, not the recommended one, which is not always in accordance with the currently prescribed daily dose (PDD). This unit makes it possible to measure the exposure of a given population to certain drugs or groups of drugs and to compare the use at an international level [11].

Analysis of drugs use allows: to confirm the quality of prescribing in terms of safety, efficiency and costs for the organization, improvement of the financial effects of therapy while reducing the costs of inappropriate use of drugs, better quality of clinical pharmacy services in terms of clinical pharmaceutical practice and educational benefits [11].

According to the data contained in the report on the financial operations of the Republic Health Insurance Fund for the year 2018, the total expenditures for the year 2018 amounted to 250,739.64 million dinars. Health care expenditures in 2018 amounted to 232,511.93 million dinars. Expenditures for drugs issued on prescription to insured persons of the Fund were made in the amount of 33,878.77 million dinars (99.91% of the plan amounting to 33,910 million dinars), which constitutes 14.57% of health care expenditures. The average expenditures of the Fund for treatment per inhabitant in 2018 are 32,353 dinars or about 275 EUR, while the average expenditures of the Fund for drugs per inhabitant in 2018 are 4,839 dinars or about 40 EUR [12].

The pharmaceutical industry of Serbia, with a share of 3.10% in the gross domestic product of the industrial sector, occupies a significant place in the economy and makes up over 50% of the chemical industry of Serbia, and the annual gross product of the pharmaceutical sector of Serbia in 2008 was over EUR

500.00 million. It is very significant that a continuous natural growth of production at an annual rate of 10-15% has been registered in this industry for several years [13].

AIM

The aim of this work was to determine drugs with the highest expenditure in the Republic of Serbia, and to compare the results obtained in three consecutive years in 2016, 2017 and 2018, as well as to analyse which are the most

expensive drugs that are in the National Medication Register and the trend of their change.

MATERIAL AND METHODS

Data on the expenditure and price of drugs in the Republic of Serbia for the period from 2016 to 2018 were taken from the official website of the Agency for Medicines and Medical Devices of the Republic of Serbia and the Republic Health Insurance Fund of Serbia [12,14,15].

The expenditure of drugs in this case was monitored using the ATC/DDD methodology. It is the classification of medications according to the internationally accepted ATC classification of medications, while DDD, i.e. defined daily dose, is used as a statistical unit for expenditure monitoring. The number of DDD/1,000 inhabitants per day provides an insight into how many inhabitants (out of 1,000 of them) used the observed medication and how many of them were exposed to its effects during one day.

Anatomical-therapeutic-chemical (ATC) classification is based on a combination of 7 alphanumeric characters that indicate the International Nonproprietary Name (INN) of the medication, or a combination of drugs. Substances are classified into groups at five levels, which makes the ATC classification possible to compile complete statistics on medication consumption at five different levels.

Data on current drugs prices for the

Table 1. Total turnover of drugs in the Republic of Serbia in the period 2004-2018 expressed in dinars and euros.

Year	RSD	EUR
2004	24,190,614,359.06	339,279,303.77
2005	32,143,911,098.04	380,716,701.39
2006	42,389,483,753.40	510,833,609.54
2007	54,690,625,906.61	687,588,174.80
2008	65,972,228,169.70	799,082,221.00
2009	71,200,588,899.80	741,981,960.19
2010	75,397,383,619.60	709,317,344.16
2011	74,003,411,597.40	722,207,154.57
2012	84,188,905,685.44	742,013,975.72
2013	91,342,622,729.08	794,560,044.61
2014	94,880,672,904.41	788,006,186.60
2015	103,561,624,361.85	851,476,036.06
2016	109,119,614,200.30	883,757,848.52
2017	116,019,995,011.07	979,319,616.87
2018	127,403,761,053.29	1,077,957,196.49

Table 2. Comparative presentation of drug consumption of individual ATC groups in the Serbia in the period from 2016 to 2018 expressed in DDD/1000 inh./day and percentages.

Year	Serbia					
	2016		2017		2018	
	DDD	%	DDD	%	DDD	%
A	236.74	14.63	171.91	11.32	212.24	13.02
B	283.59	17.52	294.20	19.37	319.64	19.61
C	635.11	39.24	624.32	41.10	658.17	40.38
D	0.19	0.01	0.19	0.01	0.24	0.02
G	40.43	2.49	42.97	2.83	40.46	2.48
H	29.45	1.82	27.83	1.83	25.74	1.58
J	30.73	1.89	25.60	1.69	25.04	1.54
L	4.93	0.30	5.32	0.35	5.69	0.35
M	66.88	4.13	84.81	5.58	69.63	4.27
N	203.35	12.56	165.29	10.88	189.08	11.60
P	0.58	0.03	0.85	0.06	0.39	0.02
R	72.00	4.45	75.88	4.99	83.56	5.13
S	14.08	0.87	0.00	0.00	0.00	0.00
V	0.06	0.00	0.06	0.00	0.06	0.00
TOTAL	1,618.17	100.00	1,519.22	100.00	1,629.94	100.00

DDD - DDD/1000 inh./day

A - Digestive tract and metabolism

B - Blood and blood-forming organs

C - Cardiovascular system

D - Dermatological drugs

G - Urogenital system and sex hormones

H - Systemic hormones without sex hormones

J - Systemic antiinfective drugs

L - Antineoplastics and immunosuppressants

M - Musculoskeletal system

N - Central nervous system

P - Medicines against parasitic infections

R - Respiratory system

S - Sensory organs

V - The others

Republic of Serbia were obtained from the official website of the Republic Health Insurance Fund.

The obtained results are presented in tables. This investigation is an academic (non-commercial) research of the IV phase.

RESULTS

Table 1 shows the total turnover of drugs in the Republic of Serbia in the period 2004-2018, expressed in dinars and euros.

Table 2 provides a comparative view of drugs expenditure per DDD per 1,000 inhabitants per day and the percentage participation of individual ATC groups in the Republic of Serbia in the period from 2016 to 2018.

Table 3 compare the drugs with the highest DDD price (over 1,000 euros) in three consecutive years, 2016, 2017 and 2018.

Table 4 list the most expensive drugs in three consecutive years, 2016, 2017 and 2018.

Tables 5-7 list the drugs for which the largest funds were spent in the Republic of Serbia in 2016, 2017 and 2018.

DISCUSSION

The total turnover of drugs for human use in the Republic of Serbia in 2018 is the highest compared to the period from 2004 to 2018. This turnover amounts to EUR 1,077,957,196.49. In 2016, it amounted to EUR 883,757,848.52 and in 2017 to EUR 979,319,616.87, showing a constant increase from year to year.

In 2016, 2017 and 2018, the highest expenditure for drugs used in the treatment of diseases of the cardiovascular system (ATC group C) was around 635.11 DDD/1000 in-

Serbia			
2016			
ATC	INN	DDD	1 DDD price in euros
B02BD08	eptacog alfa (activated)	0.000028093	30,461.57
B02BD03	anti-inhibitory complex of factor VIII	0.000025611	8,530.35
L04AC02	baziliksimab	0.00000755	1,867.50
B02BD06	von Willebrand factor and coagulation factor VIII in combination	0.000443972	1,837.67
A16AB05	laronidase	0.000105503	1,352.50
A16AB02	imiglucerase	0.000181193	1,072.68
A16AB07	alglucosidase alfa	0.000336447	1,034.86
2017			
ATC	INN	DDD	1 DDD price in euros
L03AB07	interferon beta-1a	0.211303397	12,242.27
L03AX16	plerixafor	0.000005559	3,939.11
A16AB12	elosulfase alfa	0.000010507	3,142.17
B01AB02	antithrombin III	0.000210975	3,033.69
L04AC02	basiliximab	0.000007394	1,946.31
B06AC02	icatibant	0.000038526	1,621.28
A16AB05	laronidase	0.000054481	1,409.58
A16AB02	imiglucerase	0.000474245	1,117.95
2018			
ATC	INN	DDD	1 DDD price in euros
L03AX16	plerixafor	0.000015652	3,891.29
L04AC02	basiliximab	0.000006065	1,935.71
B06AC02	icatibant	0.000030131	1,580.58
A16AB05	laronidase	0.00010174	1,286.31
A16AB02	imiglucerase	0.000590094	1,111.86
A16AB07	alglucosidase alfa	0.000180002	1,072.66

Table 3. Drugs with the highest price per DDD in euros in 2016, 2017 and 2018.

DDD - DDD/1000 inh./day

Table 4. Drugs with the highest price per package in euros in 2016, 2017 and 2018.

* - drug with the highest price per package

** - drug for which the largest funds were allocated

Serbia				
2016				
ATC	INN	Price of 1 pack	Number of packs sold	Total cost
L01XJ01	vismodegib*	820,563.40	2	1,641,126.80
L04AX04	lenalidomide**	728,064.70	27	19,657,746.90
2017				
ATC	INN	Price of 1 pack	Number of packs sold	Total cost
J05AP51	sofosbuvir, ledipasvir*	1,846,147.50	6	11,076,885.00
L01EL01	ibrutinib	902,611.60	5	4,513,058.00
L01EC02	dabrafenib**	833,631.70	54	45,016,111.80
L01EB04	osimertinib	832,820.40	7	5,829,742.80
L01XJ01	vismodegib	820,563.40	20	16,411,268.00
L01EE01	trametinib	751,061.40	54	40,557,315.60
L04AX04	lenalidomide	728,064.70	59	42,955,817.30
L01EE02	cobimetinib	700,238.60	6	4,201,431.60
L03AX16	plerixafor	666,666.00	10	6,666,660.00
L01XK04	olaparib	626,236.90	2	1,252,473.80
2018				
ATC	INN	Price of 1 pack	Number of packs sold	Total cost
J05AP51	sofosbuvir, ledipasvir*	1,831,747.50	32	58,615,920.00
J05AP08	sofosbuvir	1,633,002.90	5	8,165,014.50
J05AP53	ombitasvir, paritaprevir, ritonavir	1,458,054.70	23	33,535,258.10
J05AP54	elbasvir, grazoprevir	1,145,389.70	268	306,964,439.60
L01XG03	ixazomib	969,217.40	5	4,846,087.00
L01EB04	osimertinib	815,164.60	26	21,194,279.60
L04AX04	lenalidomide	690,403.90	257	177,433,802.30
L01ED03	alectinib	659,746.40	1	659,746.40
L03AX16	plerixafor	657,016.70	28	18,396,467.60
L01EL01	ibrutinib	652,389.70	136	88,724,999.20
L01FF05	atezolizumab	615,561.30	13	8,002,296.90
L01XK04	olaparib	606,605.50	32	19,411,376.00
L01EC02	dabrafenib	590,622.20	96	56,699,731.20
L01EE02	cobimetinib	563,704.70	37	20,857,073.90
L01EF01	palbociclib	525,601.40	2	1,051,202.80
L01ED01	crizotinib	517,090.40	43	22,234,887.20
L01EX01	sunitinib**	500,433.40	1,127	563,988,441.80

habitants/day (39.24% of total consumption) in 2016, in 2017 it was 624.32 DDD/1000 inhabitants/day (41.10%), while in 2018 it was the highest and amounted to 658.17 (40.38%). This information is correlated with the research from 2008, where a financial analysis was done in the period 2004-2007. Of the total expenditure of drugs in the Republic of Serbia, the share of drugs that affect the cardio-

vascular system was 30.54%, 30.57%, 38.26% and 36.89%, which is the highest compared to other groups of drugs [16].

There is no increase in expenditure from 2016 to 2017, which corresponds to the data that the total expenditure of drugs is lower in 2017 compared to 2016. The total expenditure in 2016 is 1,618.17 DDD/1000 inhabitants/day, in 2017 it is 1,519.22 DDD/1000

Serbia			
2016			
ATC	INN	Number of packs sold	Total cost
L01FD01	trastuzumab*	8,288	1,851,144,691.20
B01AC06	acetylsalicylic acid	7,814,960	1,725,126,211.10
A02BC02	pantoprazole	4,963,474	1,551,850,929.84
C09AA05	ramipril	4,789,710	1,478,760,339.10
C07AB07	bisoprolol	5,721,005	1,438,742,435.10
N02BE51	paracetamol, combinations	9,291,690	1,344,761,505.33
H01AC01	somatropin	32,455	1,260,832,241.90
A10AD05	insulin aspart	311,765	1,172,485,812.00
N05BA08	bromazepam**	10,768,550	1,164,923,699.20
C08CA01	amlodipine	4,890,547	1,150,365,002.30
C10AA07	rosuvastatin	844,074	1,116,374,315.40
A10BA02	metformin	7,645,052	1,096,719,774.00
C09AA02	enalapril	3,490,321	1,054,501,342.30
B05AA01	albumin	263,294	1,040,257,453.60
M01AE01	ibuprofen	5,702,362	1,020,147,048.10

Table 5. Drugs for which the largest funds were allocated in 2016.

* - drug for which the largest funds were allocated
 ** - drug with the most sold packages

inhabitants/day, while in 2018 it was the highest with 1,629.94 DDD/1000 inhabitants/day. Comparing the data on the price and expenditure of drugs in 2016, 2017 and 2018, it can be seen that the most expensive drugs from group J - anti-infective drugs for systemic use and L - antineoplastics and immunomodulators. The expenditure of these drugs in the Republic of Serbia is very low, while in the Kingdom of Norway, as a country with high quality health care, the allocated funds accounted for 27% of the total cost in 2018, which is the largest

group in terms of costs. The increase in costs for this group of drugs was 3.9% compared to 2017 [17].

By comparing the financial spending on the L group of drugs in 2017 compared to 2016, a significant increase was observed, from RSD 12,663,319,133.50 to RSD 15,300,594,924.20. A similar trend exists in neighboring countries, so in Montenegro an increase in expenditure was registered in the same period of as much as 49.98%. In Croatia, for a period of five years (from 2012 to 2016),

Serbia			
2017			
ATC	INN	Number of packs sold	Total cost
C09AA05	ramipril*	6,376,363	1,990,187,617.70
L01FD01	trastuzumab	9,558	1,988,592,354.70
B01AC06	acetylsalicylic acid	8,246,865	1,903,071,897.37
A02BC02	pantoprazole	6,172,035	1,863,236,624.80
N02BE51	paracetamol, combinations**	8,476,561	1,647,321,058.19
C07AB07	bisoprolol	5,715,876	1,419,204,492.80
H01AC01	somatropin	36,179	1,364,984,883.40
M01AB05	diclofenac	6,562,704	1,326,528,216.70
C10AA07	rosuvastatin	902,589	1,237,902,035.90
M01AE01	ibuprofen	6,085,942	1,198,478,822.70
B05AA01	albumin	286,192	1,135,036,360.20
C08CA01	amlodipine	4,133,795	1,064,823,851.40
A10BA02	metformin	6,606,834	1,003,983,901.72

Table 6. Drugs for which the largest funds were allocated in 2017.

* - drug for which the largest funds were allocated
 ** - drug with the most sold packages

Table 7. Drugs for which the largest funds were allocated in 2018.

Serbia			
2018			
ATC	INN	Number of packs sold	Total cost
L01FD01	trastuzumab*	415,501	2,172,569,421.00
B01AC06	acetylsalicylic acid	8,767,187	2,051,112,679.80
N02BE51	paracetamol, combinations**	9,839,517	2,035,096,169.38
C10AA07	rosuvastatin	1,467,246	1,840,481,640.70
A02BC02	pantoprazole	6,441,676	1,757,427,580.10
C07AB07	bisoprolol	7,260,639	1,707,132,232.10
H01AC01	somatropin	46,591	1,537,256,528.20
M01AE01	ibuprofen	6,164,422	1,393,042,763.15
L01FF02	pembrolizumab	5,484	1,294,607,963.60
A10BA02	metformin	8,310,285	1,280,963,676.50
C09AA05	ramipril	4,343,328	1,201,578,088.60
C08CA01	amlodipine	4,594,651	1,181,374,022.10
J07BC01	vaccine against hepatitis B, recombinant	201,678	1,157,248,395.60
A10AE05	insulin detemir	194,688	1,142,604,403.20
A10AD05	insulin aspart	297,374	1,109,651,081.00
B02BD02	octocog alfa	22,420	1,102,068,603.60
C09AA02	enalapril	3,311,758	1,009,524,428.00

* - drug for which the largest funds were allocated

** - drug with the most sold packages

expenditure increased by 62%, calculated at wholesale prices [18].

According to a 2016 study by the IMS Institute for Health Informatics, oncology drugs represent the group with the highest global expenditure of funds on the pharmaceutical market. The costs of oncology drugs in relation to the total costs of medications range from 2.5% in the case of India to almost 16% in the case of Germany and France [19].

Biological medicines stand out as one of the newest and most expensive types of primarily oncological, but also numerous other therapies. A biological drug is a drug with biological active substance, which means a substance produced or extracted from a biological source, for the categorization and quality control of which physical-chemical-biological tests are necessary, as well as a description of the production process and its control [20].

Biological drugs have revolutionized the outcomes of not only oncology therapy, but therapy in general. Biological drugs act selectively on a certain target, that is, on targets that are specific for neoplasms, namely those molecules that are important in malignant cells for initiating processes such as: uncontrolled growth, invasion and metastasis. For this reason, the application of this selective type of

therapy is called targeted or target therapy.

Monoclonal antibodies are used the most frequently. In addition to being used in oncological therapy, these drugs can be used for numerous other indications such as: rheumatological, gastroenterological, dermatological, endocrinological and numerous other therapies [21].

Due to the loss of patent protection for original biological drugs, the focus is increasingly on biologically similar drugs - biosimilars, they are similar in terms of quality, safety and efficiency to the original drug. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological drugs. They are a comparable copy of the original drugs, but they differ in many ways from the biological original due to the way these medicinal substances are produced. The advantage of using biosimilars is the availability of therapy to a large number of patients due to reduced prices.

However, as biological drugs are products of living cells, it is necessary to conduct numerous studies in order to prove their effectiveness and safety. Companies can invest in biological drugs, given the assumption that biosimilars will not be synthesized immediate-

ly after the expiration of patent protection, because large investments are needed to develop those that would be approved for therapy.

The use of biosimilars could be a great opportunity to improve health care by reducing the price of certain drugs and making them accessible to a larger number of patients, while preserving the quality of therapy. Due to the relatively recent development of these drugs, there are still certain barriers to their use that need to be overcome [22].

Savings achieved by using biosimilars are estimated at 25% - 75% compared to the original biological drugs [23].

The trend of drug prices was growing exponentially from 2016 to 2018. In 2016, there were only two drugs over RSD 500,000.00 per package, in 2017 the number of these drugs increased to 10, while in 2018 there were as many as 17. The most expensive drug in 2016 was vismodegib, which is used in oncological therapy of basal cell carcinoma. However, it is not on the list of drugs with a price per DDD, in contrast to it, the price of lenalidomide per box is 728,064.70 RSD, and per DDD 247.58 EUR, which ranks it among expensive drugs based only on the price of the box, not the price of DDD.

In 2017, the list of the most expensive drugs (over RSD 500,000.00 per box) was expanded by 8 drugs, namely: the combination of sofosbuvir and ledipasvir, dabrafenib, trametinib, ibrutinib, osimertinib, cobimetinib, olaparib, plerixafor.

Of all the drugs on the list, it was determined that the most expensive combination is sofosbuvir and ledipasvir in the amount of 1,846,147.50 RSD, however, due to the high cost of this combination, only 6 formulations of this drugs were sold, so the total funds allocated for this drugs are not large and amount to 11,076,885.00 RSD.

The most expensive drugs from the group of antineoplastics and immunomodulators in the same year are ibrutinib with the cost of 902,611.60 RSD and dabrafenib with the cost of 833,631.70 RSD, for which the largest funds were allocated, i.e. 45,016,111.80 RSD.

The list of drugs that cost over 500,000.00 RSD was the longest in 2018, and compared to the previous one, it was expanded by 7 more drugs, namely: sofosbuvir, the combination of ombitasvir, paritaprevir and ritonavir, the combination of elbasvir and grazoprevir, atezolizumab, sunitinib, crizo-

tinib, palbociclib, alectinib, ixazomib, while trametinib and vismodegib are no longer on the list of the most expensive ones. The largest compensation was given for sunitinib in the amount of 563,988,441.80 RSD. This drug is indicated for locally advanced and/or metastatic renal cell carcinoma (clear cell subtype), in patients with a good or intermediate prognosis, and is fully paid for by the fund. In all three years, the list of the most expensive drugs is dominated by medications used in oncology therapy, mainly monoclonal antibodies, which is understandable given that they are in the group of biological drugs that are very expensive. In other studies, it was determined that the monthly prices and incremental costs of anticancer drugs are significantly related to the year of approval and showed an average annual increase of 9% to 21% [24].

If we exclude trastuzumab, the drugs for which the largest amount of money was spent in the Republic of Serbia in 2016 are acetylsalicylic acid, for which 1,725,126,211.10 RSD was spent for the amount of 7,814,960 packages, from which it can be concluded that the reason for which large sums of money were spent is not the price but the quantity of the prescribed drug. This can be justified by the wide range of indications for this drug, some of which are: acute myocardial infarction, in patients who previously had a myocardial infarction, for the secondary prevention of stroke, in stable and unstable angina pectoris, for the prevention of thromboembolism, against pain, fevers, etc.

Some of the drugs for which large amounts of money were allocated in 2016 are bromazepam, paracetamol in combinations (with caffeine, pseudoephedrine, codeine, phenylephrine, ascorbic acid, etc.), trastuzumab, pantoprazole, amlodipine and rosuvastatin. According to the American survey from 2015, rosuvastatin was the second drug on the list of the most prescribed drugs, just below levothyroxine, which in Serbia is not even in the top 10 drugs in terms of the prescribed amount. Also, in 2016, the highest quantity of bromazepam was sold in Serbia, as much as 10,768,550, which is not the case with consumption in other years. According to data on expenditure in neighboring countries, Montenegro and Croatia, similar data are obtained. Namely, in both countries, as well as in Serbia, the most used drug is acetylsalicylic acid, and in addition to it, the consumption of ramipril,

metformin, enalapril, ibuprofen and pantoprazole is also very high in all three countries. In Croatia, in contrast to the Republic of Serbia, the most used drug from the N-diazepam group is 36.92 DDD/1000 people/day, while in the Republic of Serbia in 2016, bromazepam was prescribed in a much larger amount 37.37 DDD/1000 inhabitants/day [25].

In 2017, diclofenac was added to the list, while the most was spent for ramipril, the amount of 1,990,187,617.70 RSD, for trastuzumab 1,988,592,354.70 RSD for a very small amount compared to the other drugs on the list, from which it follows that its higher price, as well as for acetylsalicylic acid in the amount of 1,903,071,897.37 RSD, much more compared to 2016, which can be justified by the amount of 8,246,865 in which this drug was sold, more precisely, by 431,905 more than the previous year. In 2018, the use of drugs such as: insulin detemir, octocog alfa, enalapril, vaccine against hepatitis B (recombinant), pembrolizumab increased, all of which except enalapril are relatively expensive, but enalapril was included in this list for 2016 and in 2018 it was returned due to the prescription of larger quantities of this drug. The most money in 2018 was allocated for trastuzumab, as much as RSD 2,172,569,421.00. The prescription of this drug was consistently high throughout all three years, however, it increased significantly from 9,558, which was in 2017, to 415,501.5 in 2018.

Trastuzumab is intended for the treatment of breast and colon cancer. It is a monoclonal antibody and selectively binds to an antigen called human epidermal growth factor receptor 2 (HER2) and thus stops the growth of cancer cells possessing this antigen and causes their death [26]. The increased expenditure of trastuzumab can be attributed to the increased incidence of breast cancer, considering that approximately 3,700 new cases are registered in the Republic of Serbia every year. Also, the drug whose use has been growing exponentially over the years is combinations of paracetamol, and in 2018 as much as RSD 2,035,096,169.38 was spent on it.

Eptacog alfa (activated) is the drug that in 2016 had the highest DDD price in euros, which is 30,461.57 EUR. It is used in patients with congenital hemophilia who have inhibitors to factors VIII or IX, and it is introduced based on the opinion of a hematologist or internist or pediatrician in hemophilia

treatment centers. Next to it, the anti-inhibitory complex of factor VIII and von Willebrand factor and coagulation factor VIII in combination had a high price of 1 DDD for the same year, which are also used in hematological therapy, as well as enzymes: imiglucerase, laronidase and alglucosidase alfa [27]. While from the group of biological drugs, i.e. monoclonal antibodies, it is basiliximab found that its place on the list.

In 2017, in addition to basiliximab, antithrombin III and interferon beta-1a had a DDD value of more than 1,000.00 EUR among biological drugs, which had the highest DDD price for that year, which was 12,242.27 EUR.

In 2018, as in previous years, the enzymes imiglucerase, laronidase and the biological drug basiliximab had a high DDD, and the drug plerixafor had the highest price, RSD 3,891.29. Between 2016 and 2017, an increase in the DDD price of the drugs on the list was registered for all three observed years, while between 2017 and 2018, a slight drop in the price of the three drugs was registered. In 2017, the price of plerixafor per box was 666,666.00 RSD, while its price per DDD was 466,666.20 RSD, that is, 3,939.11 EUR, which is shown in Table 3. Its price per box and per DDD was high, which made it a very expensive of plerixafor. According to the Republican Fund for Health Insurance of Serbia, it belongs to the C list of drugs - those with a special dispensing regime and fully reimbursed. In 2018, the price of one of its boxes was RSD 657,016.70, while according to the DDD this price was 3,891.29 EUR, or 459,911.69 RSD. Although its price in 2018 was slightly lower compared to the previous one, it represents the drug with the highest price of DDD.

CONCLUSION

In order to use the available resources of a country in the right way, it is necessary to analyse in detail and compare the prices and outcomes of the application of new, more expensive drugs, with the price and outcome of already existing, standard therapies. In this way, it is possible to direct the available financial resources to the financing of the most profitable therapeutic strategies, as well as to rationalize the use of drugs in the population. Modern medicine relies more and more on the use of pharmacoepidemiology and pharmaco-economics methods in the management of

drugs in healthcare institutions.

In the Republic of Serbia, there is a constant increase in the turnover of drugs for human use, with the largest expenditures for the drugs used in the treatment of the cardiovascular system diseases.

The most expensive drugs in the Republic of Serbia belong to group J - anti-infective medications for systemic use and L - antineoplastics and immunomodulators, but the expenditure of these drugs in the Republic of Serbia is very low, unlike the countries with a high standard of living and high quality health care, such as in the Kingdom of Norway and the USA. The most expensive drugs in all three observed years at the price of 1 DDD are the enzymes imiglucerase, laronidase and the biological drug basiliximab, and of the biological drugs in 2017, in addition to basiliximab, antithrombin III and interferon beta-1a.

The most commonly used drugs from group L are monoclonal antibodies that belong to biological drugs and are prescribed mostly in oncology. Since these drugs are very expensive, it is believed that the introduction of biologically similar alternatives could enable increasing the availability of therapy to a large number of patients due to reduced prices.

Drugs for which the largest funds were spent in the Republic of Serbia are mainly those with a wide range of indications, such as acetylsalicylic acid, so the reason why large funds were spent on this drugs is not the price, but frequent prescribing. In addition to acetylsalicylic acid, drugs for which large amounts of money are spent are paracetamol in combinations, trastuzumab, pantoprazole and amlodipine.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Lekovi sa najvećom potrošnjom u Republici Srbiji

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KRATAK SADRŽAJ

Uvod: Politika lekova predstavlja zajednički napor da se postignu bolji zdravstveni ishodi za sve, posebno usmjavajući se na pristup ljudi i racionalnu upotrebu lekova. Na osnovu farmakoeкономskih analiza moguće je modifikovati ustaljene propisivačke navike, može se uticati na izradu smernica, strategiju razvoja i dugoročnog planiranja zdravstvene zaštite.

Cilj: Cilj rada bio je utvrditi za koje se lekove troše najveća sredstva u Republici Srbiji, te dobijene rezultate uporediti u tri uzastopne godine 2016, 2017. i 2018. Takođe, analizirati koji su najskuplji lekovi koji se nalaze u Nacionalnom registru lekova i trend menjanja istih.

Materijal i metode: Potrošnja lekova u ovom slučaju praćena je korišćenjem ATC/DDD metodologije. Ona podrazumeva klasifikaciju lekova prema međunarodno prihvaćenoj ATC klasifikaciji lekova, dok se DDD tj. definisana dnevna doza, koristi kao statistička jedinica praćenja potrošnje. Broj DDD/1000 stanovnika na dan omogućava uvid u to koliki je broj stanovnika (od njih 1000) koristio posmatrani lek i bio izložen njegovom delovanju tokom jednog dana.

Rezultati: Trend kretanja cena lekova raste eksponencijalno od 2016. do 2018. godine. Najskuplji lekovi po kutiji su iz grupe J-antiinfektivni lekovi za sistemsku upotrebu i L- antineoplastici i imunomodulatori, ali je njihova potrošnja u Republici Srbiji vrlo niska. Lekovi sa najvišom cenom po 1 DDD-u su: enzimi imigluceraza, laronidaza i biološki lek baziliksimumab u sve tri godine, ali s obzirom na indikacije i retkost njihovog propisivanja ukupni trošak za ove lekove nije veliki. Najveća novčana sredstva u Republici Srbiji za pomenuti period utrošena su za lekove kao što su: acetilsalicilna kiselina, paracetamol u kombinacijama, trastuzumab, pantoprazol, amlodipin i rosuvastatin. Poređenjem finansijske potrošnje na L grupu lekova u 2017. u odnosu na 2016. godinu desio se značajan porast.

Zaključak: Najskuplji lekovi u Republici Srbiji se vrlo malo koriste u odnosu na zemlje sa dobrom farmakoterapijskom praksom. Najskuplji lekovi su oni koji se koriste za posebne i retke indikacije te se za njih ne izdvajaju velike količine novca kao za neke jeftinije, ali češće propisivanije lekove.

Ključne reči: potrošnja lekova, najskuplji lekovi, cena leka

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