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CONSUMPTION ANALYSIS OF TWO-COMPONENT FIXED COMBINATIONS OF MEDICINES FOR ARTERIAL HYPERTENSION TREATMENT IN UKRAINE AS ONE OF THE STAGES FOR EVALUATION OF THEIR REIMBURSEMENT PROSPECTS

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The aim was to conduct a retrospective consumption analysis of 4 groups of single pill combinations for hypertension treatment and identify potential candidates for future inclusion in the reimbursement list in Ukraine, based on retrospective consumption patterns.

Materials and methods. The objects of the study were retail sales data in pharmaceutical market in Ukraine of four groups of single pill combinations used for arterial hypertension treatment. Data was provided by the marker research system “Pharmstandard” of the company of “Morion”. Analytic-comparative, systematic, logical, and mathematical-statistical methods were used.

Results. Single pill combinations of ACE inhibitors with diuretics were the most consumed among other combinations on 2018–2020. Retrospective evaluation of consumption patterns in period of 2018–2020 showed that combinations of captopril and hydrochlorothiazide (HCTD) 50 mg/25 mg, enalapril and HCTD 10 mg/25 mg, lisinopril and HCTD 10 mg/12.5 mg were the most consumed. Among ARB and diuretics combinations valsartan and HTCD (160 mg/12.5 mg and 80 mg/12.5 mg) and losartan and HTCD (50 mg /12.5 mg) were the most consumed among ARB and diuretics combinations. Within ACE inhibitors and calcium channel blockers (CCB) combinations the most consumed were lisinopril/amlodipine 10 mg/5 mg and a perindopril arginine/amlodipine 5 mg/5 mg. Valsartan and amlodipine holds the majority among ARC and CCB combinations, consumed in period of 2018–2020.

Conclusion. Apart from the single pill combinations, enlisted in the WHO Essential medicines list, eight more single pill combination were identified, based on retrospective consumption patterns, as potential candidates for further inclusion in the reimbursement list in Ukraine

Keywords: arterial hypertension, single pill combination, consumption patterns, reimbursement, pharmaceutical market

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1. Introduction

In 2019, the number of people with hypertension in the world was more than 1 billion people, and their number increased twice compared to 1990 [1]. Hypertension is the main, but at the same time preventable, risk factor for the development of cardiovascular diseases (CVD) and is responsible for 55 % of deaths caused by coronary heart disease and 45 % of deaths caused by cerebrovascular diseases [2]. Prevention, control and treatment of CVD and hypertension require long-term treatment, where constant (physical availability and socio-economic affordability) of medicines is critical. Despite the proven effectiveness of drugs that lower blood pressure (BP), regarding BP control as well as prevention of CVD complications, their use is markedly insufficient – which leads to sub-optimal BP control at the population level [3, 4]. Up to 50–70 % of patients need combined therapy, which is determined using at least two drugs, to achieve the target BP [5]. However, the complexity of treatment strategies could affect treatment adherence, which is strongly influenced by the number of

pills that are prescribed to the patient [6]. With one pill, patient nonadherence to treatment reaches up to 10 %, and increases to 20 % if the patient must take two pills, and rises to 40 % with three pills, and rises to very high values, up to complete refusal of treatment among patients, who are prescribed five or more tablets [6]. CVDs are also associated with low adherence to treatment [7]. Given these reasons, the 2018 European Society of Cardiology Hypertension Clinical Guideline encourages the use of combination therapy in most patients, especially in the context of reduced BP targets, and allows the use of combination drugs in one pill for most patients to improve adherence. Basic strategy of medical treatment of uncomplicated arterial hypertension (AH) offers a double combination of angiotensin-converting enzyme inhibitor (iACE) or angiotensin receptor blocker (ARB) with calcium channel blockers (CCB) or diuretics as initial therapy [8]. This clinical guideline is approved for use in medical practice in Ukraine [9].

CVD is the main cause of death (64.3 %) among the adult population of Ukraine [10], so a priority issue in

the field of health care in developing countries is to increase the availability of medicines used to treat socially important diseases [11]. For low- and middle-income countries like Ukraine, high price and low availability are the main barriers to the use and adherence to the main medicines for the treatment of CVD and AH [12, 13].

In 2017, the state program “Affordable Medicines” was implemented by the government of Ukraine to achieve the goal of affordable, fair and permanent access to medicines for the treatment of CVD, type 2 diabetes and bronchial asthma [14, 15]. The program was developed according to the concept. An exemplary list of essential medicines (EM) that was proposed by WHO to meet WHO’s requirements to ensure access to medicines, especially for the treatment of CVD [16, 17]. In 2019 the WHO sample list of EM was supplemented with 4 combined EM for the treatment of AH - lisinopril/amlodipine (10 mg/5 mg, 20 mg/5 mg, 20 mg/10 mg), lisinopril/hydrochlorothiazide (HCTD) (10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg), telmisartan/amlodipine (40 mg/5 mg, 80 mg/5 mg, 80 mg/10 mg) and telmisartan/HCTD (40 mg/12.5 mg, 80 mg/12.5 mg, 80 mg/25 mg), which, considering active substances and doses, makes 12 combinations [18]. But none of these combined medicines were included in the list of pharmaceuticals subject to reimbursement under the state program “Affordable Medicines” and the National List of Medicines of Ukraine after the update of WHO Model List of Medicines in 2019 [19].

Today, modern European clinical guidelines for the treatment of AH [8] provide for the use of combined medicines, from the very beginning of treatment, their absence in the National List of Medicines [20] and, accordingly, in the “Affordable Medicines” program, create the need to develop tangible, specific and adapted proposals for combined pharmaceuticals at the national level for further possible clinical and economic studies on their use and subsequent discussion on their inclusion in reimbursement programs in Ukraine.

The aim: to conduct a retrospective study of the consumption of 4 groups of combined medicines and determine their structure, considering the active substances and their doses, to determine the most consumed fixed doses of combined drugs for the purpose of developing proposals for further clinical and economic studies on their use in the context of expanding the list of medicines that are subject to reimbursement, with the help of including combined drugs for the treatment of AH.

2. Planning (methodology) of the research

To achieve the aim of the study, the following research stages were planned:

– I – analysis of modern information sources, which present data on the consumption analysis of combined medicines used in the treatment of AH in different countries of the world, collection and formation of a statistical research base, namely retail sales of antihypertensive two-component combined medicines iACE and diuretics, iACE and CCB, ARB and diuretics, ARB and CCB on the pharmaceutical market of Ukraine in the

period from 2018 to 2020 to determine the structure of their consumption according to the ATC classification and in accordance with the WHO methodology, relatively to the UD indicator.

– II – to estimate the consumption of each combined medicine according to unit dose (UD) indicators, considering the number of active ingredients and their doses. This indicator makes it possible, according to the current WHO methodology, to analyze the structure of the consumption of combined medicines considering only the number of tablets, not taking into account the composition of the combined pharmaceutical according to the INN, and the dose of active substances.

The proposed stage of the study represents an innovative way of obtaining a more detailed structure of the consumption of combined medicines for the treatment of AH, which, in our opinion, is a logical and consistent addition to the existing WHO methodology [21] regarding studies of the consumption of combined pharmaceuticals.

– III – calculate the proportion of consumption of each dose of a fixed combination within the study group (iACE and diuretic; iACE and CCB; ARB and diuretic; ARB and CCB) for each year separately and its median over three years and identify those fixed combinations that had the greatest values consumption share medians over three years. And recommend them for conducting clinical and economic studies in the context of discussing the issue of expanding the list of combined medicines for the treatment of AH that are subject to reimbursement in Ukraine.

3. Materials and methods

The object of the study was retail sales data provided by the “Pharmxplorer” market research system of the “Proxima Research” company [22]. Retail sales data are the objects of studies on medicine consumption in accordance with the approved WHO methodology. Retail sales data were structured according to the 4th and 5th level of the ATC classification, and included the following ATC groups C09BA 01-15, C09BB 02-12, C09DA 01-10, C09DB01-09. According to the WHO Guideline on the ATC classification and determination of the daily dose of medicine (DDM), in studies of the structure of consumption of combined drugs, or drugs, where the DDM indicator due to many reasons cannot be provided in the form of the number of active ingredients, including for combined drugs for treatment of AH, the unit dose (UD) indicator is used, which is equal to 1 tablet of the combined medicine for the treatment of AH [21]. Therefore, the data were loaded in packages, according to the stock keeping unit (SKU) indicator for each 5th level of ATC classification, which details the number of tablets in each package of pharmaceuticals. The total number of tablets, and accordingly the number of UD for each 5th level of ATC classification, was calculated as follows – the number of SKUs multiplied by the number of tablets contained in each SKU.

It is worth noting that according to the WHO Guidelines on the possibility of using the ATC for classification and determination of the daily dose of drugs for combined drugs (C09BA 01-15 and C09DA 01-10), the

INN of the diuretic included in the combined drug is not indicated. Also, the methodology of drug consumption analysis proposed by WHO does not consider all dosage variations of combined drugs for the treatment of AH and counts them as one UD equal to 1 tablet, regardless of the number of active substances and their doses.

Therefore, according to the data of the State Register of Medicines of Ukraine, as of January 1, 2021 [23], the content and doses of active ingredients in each SKU were determined. The obtained data on the amount of UD consumed in each SKU were summarized according to the 5th level of the ATC classification, and then structured into researched groups according to the 4th level of the ATC classification. We studied 4 groups of combined drugs according to the 4th level of the ATC classification, namely: C09BA – iACE and diuretics, C09BB – iACE and calcium channel blockers, C09DA – ARB and diuretics, C09DB – ARB and calcium channel blockers. These four groups of combinations are recommended by modern European clinical guidelines for the treatment of AH as priority for the initial and maintenance therapy of AH [24]. Subsequently, the obtained data were structured, considering the number of active substances (according to the INN) and their doses within the 4th level of the ATC classification. The share of consumption of the studied (repeat the words, paraphrase) dose of a fixed combination of drugs was calculated according to the total number of consumed UD within each studied group according to the 4th level of the ATC classification for each year separately. At the end of the analysis of the structure of drug consumption, the median share of consumption of each fixed dose over three years was determined, because this indicator makes it possible to gain an understanding of the central tendency of the distribution of data shares of consumption according to a certain variable in time [25].

Statistical data processing was carried out on computer equipment, using the Statistica software (version 12.0, StatSoft, Tulsa, USA) by the method of cluster analysis. A p -value<0.05 was defined as statistically significant. The research used statistical and mathematical methods, as well as content analysis, comparative, logical and systematic analysis, and data summarization.

4. Research results

The results of data processing of retail sales of antihypertensive two-component combined drugs, according to the 4th level of the ATC classification, on the pharmaceutical market of Ukraine, according to the UD indicator in the period from 2018 to 2020, showed that the total number of consumed combined iACE medicines and diuretics was 323,548,001 UD in 2018, 334,257,009 UD in 2019, and 325,366,459 UD in 2020. Consumption of combined iACE and CCB medicines was 42,240,680 UD, 48,330,118 UD, and 46,763,064 UD in 2018, 2019, and 2020, respectively. Regarding combined ARBs and diuretics, the number of UD consumed was 94,858,456 in 2018, 95,582,426 in 2019, and 96,784,366 in 2020. And the consumption of ARB and CCB combinations was at 29,147,534 UD in 2018, 32,117,530 UD and 35,509,272 UD in 2019 and 2020, respectively.

These data show that combined medicines of iACE and diuretics were the largest group among two-component combined pharmaceuticals consumed by Ukrainian patients between 2018 and 2020 inclusive, and had a consumption share of 66.06 %; 65.5 % and 64.5 % for the year, respectively. Combinations of ARBs and diuretics occupy the second position in the share of consumption for the corresponding period (19.37 %; 18.73 % and 19.19 % per year, respectively). The share of consumption of combinations of iACE and CCB was only 8.62 %; 9.47 % and 9.27 % per year. Combinations of ARBs and CCBs were the least consumed during this period, with only 5.95 %; 6.29 % and 7.04 % share of consumption in each year, respectively.

The results of data processing of retail sales of antihypertensive two-component combined medicines, according to the 4th and 5th level of the ATC classification, on the pharmaceutical market of Ukraine, according to the UD indicator in the period from 2018 to 2020, are presented in Table 1.

As can be seen from Table 1, among combinations of iACE and diuretics, in the period 2018–2020, the most consumed were combinations of diuretics with captopril (32.93 % in 2018; 32.65 % in 2019 and 32.9 % in 2020) enalapril (26.3 %; 23 %; 19.9 % in 2018, 2019 and 2020, respectively), lisinopril (24 % in 2018; 22.9 % in 2019 and 21.9 % in 2020), and perindopril (14.94 % in 2018; 19.65 % in 2019 and 23.54 % in 2020). However, consumption of combined enalapril with diuretics decreased year-over-year, by 8,137,786 UD (9.5 %) in 2019 compared to 2018, and by 12,268,774 UD (15.9 %) in 2020 compared to 2019. The same dynamics were observed with combined drugs of lisinopril with diuretics, in 2019 by 1.7 % compared to 2019, and by 6.8 % compared to 2020. At the same time, the consumption of combinations of perindopril with diuretics increased every year, in 2019 by 35.8 % compared to the previous year, and by 16.5 % in 2020 compared to 2019. Use of valsartan and diuretics was the highest (72 % in 2018, 67.4 % and 67.5 % in 2019 and 2020, respectively) among all combined medicines of ARBs and diuretics. Consumption of losartan/diuretic combinations decreased by 2,469,130 UD (11.2 %) in 2020 compared to the previous year, but consumption of ARB/diuretic combinations other than valsartan/diuretic combinations increased year over year. Nevertheless, these data do not allow us to clearly understand what type of diuretics according to the INN was part of these combinations.

Data on consumption of iACE and CCB combinations show that combinations of lisinopril with amlodipine and perindopril with amlodipine were the most consumed among Ukrainian patients in 2018–2020. And combinations of valsartan with amlodipine were consumed the most (99.6 % in 2018, 98.9 % in 2019 and 97.7 %) among all ARB and CCB combinations consumed in 2018–2020. The dynamics of growth is noted among combinations of enalapril and lercanidipine (24.4 % in 2019 and 2.1 % in 2020), perindopril and amlodipine (14.7 % in 2019 and 2.2 % in 2020), and ramipril with amlodipine (42.3 % in 2019 and 1.5 % in 2020), as well as among all combined ARB medicines and CCB.

Thus, it could be stated that in Ukraine the structure of consumption of combined AH pharmaceuticals is dynamic and heterogeneous, with the predominant consumption of combined iACE medicines and diuretics.

The second stage of the study involved determining the consumption of combined medicines according to the UD indicator, considering the active substances (according to the INN) and their doses. The obtained data were used to perform the third stage of the study, namely, to calculate the proportion of consumption of each fixed combination within the study group (iACE and diuretic; iACE and CCB; ARB and diuretic; ARB and CCB) for each year separately.

The results of consumption of fixed-dose combinations of iACE and diuretics are presented in Table 2.

Data from Table 2 shows that the most consumed were fixed doses of combinations of captopril with hydrochlorothiazide (HCTD) 50 mg/25 mg, the median share of consumption was 29.35 %; enalapril and HCTD 10 mg/25 mg (15.89 %) and lisinopril with HCTD 10 mg/12.5 mg (14.28 %).

Next, consumption of fixed-dose combinations of ARBs with diuretics was evaluated, and the results are presented in Table 3.

From the data presented in Table 3, we could see that the combination of valsartan and HCTD 160 mg/12.5 mg

occupied 40.65 %; 40.75 % and 39.32 % respectively in 2018, 2019, 2020. Shares of consumption among all fixed-dose combinations of ARBs and diuretics during 2018–2020. The second most consumed was the fixed dose combination of valsartan with HCTD 80 mg/12.5 mg, (26.5 %; 24.72 %; 26.24 % respectively in 2018, 2019, 2020). The third was a fixed dose combination of losartan with HCTD 50 mg/12.5 mg, with a share of consumption (18.55 %; 18.86 %; 18.40 % in 2018, 2019 and 2020, respectively).

Continuing with the second phase of the study, the consumption of fixed-dose combinations of iACE and CCB, as well as ARB and CCB combinations, was evaluated and the results are presented in Tables 4, 5, respectively.

As could be seen from Table 4, year by year the largest share (agreed) of consumption among iACE and CCB combinations belongs to the fixed-dose combination of lisinopril with amlodipine 10 mg/5 mg – 38.78 % in 2018, 36.60 % and 34.36 % in 2019 and 2020, respectively. The second place in terms of consumption is the fixed dose combination of perindopril arginine and amlodipine 5 mg/5 mg, occupying more than 10 % each year. Almost half of all ARB and CCB combinations consumed are valsartan and amlodipine 160 mg/5 mg, and more than 30 % of consumption each year is the fixed dose valsartan/amlodipine 80 mg/5 mg combination

Table 1

The results of processing and summarizing data on the consumption of antihypertensive two-component combined drugs, in Ukraine in 2018–2020, according to the UD indicator in accordance with the 5th and 4th levels of the ATC classification, according to the WHO methodology

No.	ATC classification level 5 (INN)	ATC code	UD Consumed per year		
			2018	2019	2020
The structure of consumption of combined medicines belonging to the 4 th level of the ATC classification C09BA (iACE and diuretics)					
1	Captopril and diuretics	C09BA01	106,556,180	109,163,420	107,052,540
2	Enalapril and diuretics	C09BA02	85,107,949	76,970,163	64,701,389
3	Lisinopril and diuretics	C09BA03	77,865,104	76,526,588	71,263,916
4	Perindopril and diuretics	C09BA04	48,358,860	65,696,570	76,592,610
5	Ramipril and diuretics	C09BA05	4,850,726	5,316,940	5,239,372
6	Quinapril and diuretics	C09BA06	474,180	452,490	380,160
7	Fosinopril and diuretics	C09BA09	235,350	15,870	0
8	Zofenopril and diuretics	C09BA15	99,652	114,968	136,472
The structure of consumption of combined medicines belonging to the 4 th level of the ATC classification C09BB (iACE and CCB)					
1	Enalapril and lercanidipine	C09BB02	310,604	411,180	420,028
2	Lisinopril and amlodipine	C09BB03	19,351,970	20,260,070	18,473,730
3	Perindopril and amlodipine	C09BB04	18,647,820	21,881,220	22,391,490
4	Enalapril and nitrendipine	C09BB06	1,332,360	1,268,190	899,250
5	Ramipril and almodipine	C09BB07	2,597,926	4,509,458	4,578,566
The structure of consumption of combined medicines belonging to the 4 th level of the ATC classification C09DA (ARB and diuretics)					
1	Losartan and diuretics	C09DA01	21,401,510	22,042,550	19,573,420
2	Valsartan and diuretics	C09DA03	68,386,444	64,461,976	65,410,550
3	Irbesartan and diuretics	C09DA04	1,472,488	2,366,432	2,529,860
4	Candesartan and diuretics	C09DA06	2,407,440	3,986,550	4,265,340
5	Telmisartan and diuretics	C09DA07	475,818	1,073,562	2,479,372
6	Olmesartan medoxomil and diuretics	C09DA08	177,828	283,052	447,244
7	Azilsartan medoxomil and diuretics	C09DA09	536,928	1,368,304	2,078,580
The structure of consumption of combined medicines belonging to the 4 th level of the ATC classification C09DB (ARB and CCB)					
1	Valsartan and amlodipine	C09DB01	29,035,478	31,767,026	34,721,234
2	Olmesartan medoxomil and amlodipine	C09DB02	112,056	350,504	695,128
3	Telmisartan and amlodipine	C09DB04	0	0	92,910

Table 2

Consumption of fixed-dose combinations of iACE and diuretics in Ukraine in 2018-2020

No.	ATC code of the 5 th level	INN	AI doses (mg)	UD Consumed per year, considering the number of active substances and doses, and the share in the group, %			Median share of consumption over three years, %
				2018	2019	2020	
1	C09BA01	Captopril and hydrochlorothiazide	50/12.5	9,794,080, 3.03 %	11,057,020, 3.31 %	11,920,340, 3.66 %	3.31 %
2	C09BA01	Captopril and hydrochlorothiazide	50/25	96,762,100, 29.91 %	98,106,400, 29.35 %	95,132,200, 29.24 %	29.35 %
3	C09BA02	Enalapril and hydrochlorothiazide	5/12.5	0, 0.00 %	20, 0.00 %	260, 0.00 %	0.00 %
4	C09BA02	Enalapril and hydrochlorothiazide	10/12.5	21,226,010, 6.56 %	19,376,900, 5.80 %	16,332,220, 5.02 %	5.80 %
5	C09BA02	Enalapril and hydrochlorothiazide	10/25	55,163,640, 17.05 %	53,101,540, 15.89 %	45,438,530, 13.97 %	15.89 %
6	C09BA02	Enalapril and hydrochlorothiazide	20/12.5	2,998,664, 0.93 %	2,893,108, 0.87 %	2,594,904, 0.80 %	0.87 %
7	C09BA02	Enalapril and indapamide	10/2.5	3,410,685, 1.05 %	509,685, 0.15 %	138,780, 0.04 %	0.15 %
8	C09BA02	Enalapril and indapamide	20/2.5	2,308,950, 0.71 %	1,088,910, 0.33 %	196,695, 0.06 %	0.33 %
9	C09BA03	Lisinopril and hydrochlorothiazide	10/12.5	48,655,958, 15.04 %	47,730,332, 14.28 %	44,295,528, 13.61 %	14.28 %
10	C09BA03	Lisinopril and hydrochlorothiazide	20/12.5	29,209,146, 9.03 %	28,796,256, 8.62 %	26,968,388, 8.29 %	8.62 %
11	C09BA04	Perindopril tert-butylamine and indapamide	2/0.625	592,080, 0.18 %	865,020, 0.26 %	1,045,680, 0.32 %	0.26 %
12	C09BA04	Perindopril arginine and indapamide	2.5/0.625	5,548,320, 1.71 %	6,237,690, 1.87 %	6,692,190, 2.06 %	1.87 %
13	C09BA04	Perindopril tert-butylamine and indapamide	4/1.25	8,631,420, 2.67 %	12,890,850, 3.86 %	16,839,420, 5.18 %	3.86 %
14	C09BA04	Perindopril arginine and indapamide	5/1.25	1,1651,370, 3.60 %	13,929,330, 4.17 %	13,289,370, 4.08 %	4.08 %
15	C09BA04	Perindopril tert-butylamine and indapamide	8/2.5	14,414,400, 4.46 %	22,161,110, 6.63 %	28,076,160, 8.63 %	6.63 %
16	C09BA04	Perindopril arginine and indapamide	10/2.5	7,521,270, 2.32 %	9,612,570, 2.88 %	10,649,790, 3.27 %	2.88 %
17	C09BA05	Ramipril and hydrochlorothiazide	2.5/12.5	331,044, 0.10 %	364,298, 0.11 %	293,262, 0.09 %	0.10 %
18	C09BA05	Ramipril and hydrochlorothiazide	5/12.5	929,464, 0.29 %	1,101,140, 0.33 %	1,180,672, 0.36 %	0.33 %
19	C09BA05	Ramipril and hydrochlorothiazide	5/25	2,335,638, (0.72 %)	2,895,804, (0.87 %)	2,916,092, (0.90 %)	0.87 %
20	C09BA05	Ramipril and hydrochlorothiazide	10/12.5	1,202,500, 0.37 %	954,558, 0.29 %	848,446, 0.26 %	0.29 %
21	C09BA05	Ramipril and hydrochlorothiazide	10/25	52,080, 0.02 %	1,140, 0.01 %	900, 0.01 %	0.00 %
22	C09BA06	Quinapril and hydrochlorothiazide	10/12.5	220,800, 0.07 %	213,990, 0.06 %	166,260, 0.05 %	0.06 %
23	C09BA06	Quinapril and hydrochlorothiazide	20/12.5	253,380, 0.08 %	238,500, 0.07 %	213,900, 0.07 %	0.07 %
24	C09BA09	Fosinopril and hydrochlorothiazide	20/12.5	235,350, 0.07 %	15,870, 0.00 %	0, 0.00 %	0.00 %
25	C09BA15	Zofenopril and hydrochlorothiazide	30/12.5	99,652, 0.03 %	114,968, 0.03 %	136,472, 0.04 %	0.03 %

Table 3

Consumption of fixed-dose combinations of ARBs and diuretics in Ukraine in 2018–2020

No.	ATC code of the 5 th level	Active ingredients (INN)	AI doses (mg)	UD Consumed in a year, and share in the group, %			Median share of consumption over three years, %
				2018	2019	2020	
1	C09DA01	Losartan and hydrochlorothiazide	50/12.5	17,598,780, 18.55 %	18,030,840, 18.86 %	17,804,280, 18.40 %	18.55 %
2	C09DA01	Losartan and hydrochlorothiazide	100/12.5	726,990, 0.77 %	997,020, 1.04 %	842,010, 0.87 %	0.87 %
3	C09DA01	Losartan and hydrochlorothiazide	100/25	3,075,740, 3.24 %	3 014,690, 3.15 %	927,130, 0.96 %	3.15 %
4	C09DA03	Valsartan and hydrochlorothiazide	80/12.5	25,137,358, 26.50 %	23,627,434, 24.72 %	25,399,282, 26.24 %	26.24 %
5	C09DA03	Valsartan and hydrochlorothiazide	160/12.5	38,557,894, 40.65 %	38,949,538, 40.75 %	38,055,438, 39.32 %	40.65 %
6	C09DA03	Valsartan and hydrochlorothiazide	160/25	3,758,738, 3.96 %	1,289,296, 1.35 %	1,387,486, 1.43 %	1.43 %
7	C09DA03	Valsartan and hydrochlorothiazide	320/12.5	590,308, 0.62 %	386,726, 0.40 %	368,882, 0.38 %	0.40 %
8	C09DA03	Valsartan and hydrochlorothiazide	320/25	342,146, 0.36 %	208,982, 0.22 %	199,462, 0.21 %	0.22 %
9	C09DA04	Irbesartan and hydrochlorothiazide	150/12.5	738,126, 0.78 %	1,059,744, 1.11 %	1,292,006, 1.33 %	1.11 %
10	C09DA04	Irbesartan and hydrochlorothiazide	300/12.5	734,362, 0.77 %	1,306,688, 1.37 %	1,237,854, 1.28 %	1.28 %
11	C09DA06	Candesartan and hydrochlorothiazide	16/12.5	1,455,330, 1.53 %	2,309,670, 2.42 %	2,362,920, 2.44 %	2.42 %
12	C09DA06	Candesartan and hydrochlorothiazide	32/25	952,110, 1.00 %	1,676,880, 1.75 %	1,902,420, 1.97 %	1.75 %
13	C09DA07	Telmisartan and hydrochlorothiazide	40/12.5	24,472, 0.03 %	155,666, 0.16 %	477,596, 0.49 %	0.16 %
14	C09DA07	Telmisartan and hydrochlorothiazide	80/12.5	451,346, 0.48 %	834,540, 0.87 %	1,786,792, 1.85 %	0.87 %
15	C09DA07	Telmisartan and hydrochlorothiazide	80/25	0, 0.00 %	83,356, 0.09 %	214,984, 0.22 %	0.09 %
16	C09DA08	Olmesartan medoxomil and hydrochlorothiazide	20/12.5	130,172, 0.14 %	233,380, 0.24 %	354,256, 0.37 %	0.24 %
17	C09DA08	Olmesartan medoxomil and hydrochlorothiazide	20/25	47,656, 0.05 %	49,672, 0.05 %	84,980, 0.09 %	0.05 %
18	C09DA08	Olmesartan medoxomil and hydrochlorothiazide	40/12.5	0, 0.00 %	0, 0.00 %	8,008, 0.01 %	0.00 %
19	C09DA09	Azilsartan medoxomil and hydrochlorothiazide	40/12.5	370,888, 0.39 %	712,460, 0.75 %	1,370,908, 1.42 %	0.75 %
20	C09DA09	Azilsartan medoxomil and hydrochlorothiazide	40/25	166,040, 0.18 %	655,844, 0.69 %	707,672, 0.73 %	0.69 %

Table 4

Consumption of fixed-dose combinations of iACE and CCB in Ukraine in 2018–2020

No.	ATC code of the 5 th level	Active ingredients (INN)	AI doses (mg)	UD Consumed in a year, and share in the group, %			Median share of consumption over three years, %
				2018	2019	2020	
1	2	3	4	5	6	7	8
1	C09BB02	Enalapril and lercanidipine	10/10	140,448, 0.33 %	212,016, 0.44 %	208,852, 0.45 %	0.44 %
2	C09BB02	Enalapril and lercanidipine	20/10	170,156, 0.40 %	199,164, 0.41 %	211,176, 0.45 %	0.41 %
3	C09BB03	Lisinopril and amlodipine	5/5	1,091,220, 2.58 %	405,030, 0.84 %	255,960, 0.55 %	0.84 %
4	C09BB03	Lisinopril and amlodipine	10/5	16,380,200, 38.78 %	17,688,590, 36.60 %	16,066,650, 34.36 %	36.60 %
5	C09BB03	Lisinopril and amlodipine	20/5	258,510, 0.61 %	430,290, 0.89 %	314,370, 0.67 %	0.67 %
6	C09BB03	Lisinopril and amlodipine	20/10	1,622,040, 3.84 %	1,736,160, 3.59 %	1,836,750, 3.93 %	3.84 %

Continuation of Table 4

1	2	3	4	5	6	7	8
7	C09BB04	Perindopril arginine and amlodipine	3.5/2.5	430,620, 1.02 %	54,150, 0.11 %	150, 0.00 %	0.11 %
8	C09BB04	Perindopril tert-butylamine and amlodipine	4/5	2,033,280, 4.81 %	2,876,280, 5.95 %	3,624,960, 7.75 %	5.95 %
9	C09BB04	Perindopril arginine and amlodipine	5/5	5,601,180, 13.26 %	6,655,680, 13.77 %	6,647,220, 14.21 %	13.77 %
10	C09BB04	Perindopril arginine and amlodipine	7/5	257,850, 0.61 %	146,790, 0.30 %	180, 0.01 %	0.30 %
11	C09BB04	Perindopril tert-butylamine and amlodipine	4/10	253,650, 0.60 %	327,330, 0.68 %	332,010, 0.70 %	0.68 %
12	C09BB04	Perindopril arginine and amlodipine	5/10	1,070,040, 2.53 %	1,215,390, 2.51 %	1,158,960, 2.48 %	2.51 %
13	C09BB04	Perindopril tert-butylamine and amlodipine	8/5	1,148,220, 2.72 %	1,390,800, 2.88 %	1,615,530, 3.45 %	2.88 %
14	C09BB04	Perindopril tert-butylamine and amlodipine	8/10	1,648,380, 3.90 %	2,234,970, 4.62 %	2,475,000, 5.29 %	4.62 %
15	C09BB04	Perindopril arginine and amlodipine	10/5	2,378,910, 5.63 %	2,784,390, 5.76 %	2,783,700, 5.95 %	5.76 %
16	C09BB04	Perindopril arginine and amlodipine	10/10	3,757,530, 8.90 %	4,160,220, 8.61 %	3,753,510, 8.03 %	8.61 %
17	C09BB04	Perindopril arginine and amlodipine	14/10	68,160, 0.16 %	35,220, 0.07 %	270, 0.01 %	0.07 %
18	C09BB06	Enalapril and nitrendipine	10/20	1,332,360, 3.15 %	1,268,190, 2.62 %	899,250, 1.92 %	2.62 %
19	C09BB07	Ramipril and amlodipine	5/5	1,417,084, 3.35 %	2,256,062, 4.67 %	2,466,480, 5.27 %	4.67 %
20	C09BB07	Ramipril and amlodipine	5/10	275,842, 0.65 %	408,942, 0.85 %	390,314, 0.82 %	0.83 %
21	C09BB07	Ramipril and amlodipine	10/5	680,974, 1.61 %	1,335,900, 2.76 %	1,256,360, 2.69 %	2.69 %
22	C09BB07	Ramipril and amlodipine	10/10	224,026, 0.53 %	508,554, 1.05 %	465,412, 1.00 %	1.00 %

Table 5

Consumption of fixed-dose ARB and CCB combinations in Ukraine in 2018-2020

No.	ATC code of the 5 th level	Active ingredients (INN)	AI doses (mg)	UD Consumed in a year, and share in the group, %			Median share of consumption over three years, %
				2018	2019	2020	
1	C09DB01	Valsartan and amlodipine	80/5	10,401,796, 35.69 %	10,279,616, 32.01 %	11,155,176, 31.41 %	32.01 %
2	C09DB01	Valsartan and amlodipine	160/5	13,460,714, 46.18 %	14,899,228, 46.39 %	16,508,012, 46.49 %	46.39 %
3	C09DB01	Valsartan and amlodipine	160/10	5,172,968, 17.75 %	6,588,182, 20.51 %	7,058,046, 19.88 %	19.88 %
4	C09DB02	Olmesartan medoxomil and amlodipine	20/5	52,528, 0.18 %	144,928, 0.45 %	382,200, 1.08 %	0.45 %
5	C09DB02	Olmesartan medoxomil and amlodipine	40/10	59,528, 0.20 %	205,576, 0.64 %	312,928, 0.88 %	0.64 %
6	C09DB04	Telmisartan and amlodipine	40/5	0, 0.00 %	0, 0.00 %	30,210, 0.09 %	0.09 %
7	C09DB04	Telmisartan and amlodipine	80/5	0, 0.00 %	0, 0.00 %	38,700, 0.11 %	0.11 %
8	C09DB04	Telmisartan and amlodipine	80/10	0, 0.00 %	0, 0.00 %	24,000, 0.07 %	0.07 %

5. Discussion of research results

Studies of medicine consumption for the treatment of AH, which were conducted in South Korea, show that the leading positions in the structure of consumption for the treatment of AH among combined pharmaceuticals are occupied by combinations of ARB with diuretics and ARB with CCB [26]. Studies by Japanese authors indicate that the main share of the consumption of combined medicines for the treatment of AH among Japanese patients is also occupied by combinations of ARBs with diuretics or CCBs [27]. But in these works, foreign authors do not detail the consumption of fixed doses of antihypertensive combined medicines by the number of active ingredients and their doses. According to the results of our research, it was established that in Ukraine, combinations of iACE and diuretics, and ARB and diuretics occupy leading positions in the structure of consumption. The presented results of the research allow to detail the structure of consumption of combined medicines for AH, consider-

nations of ARBs with diuretics or CCBs [27]. But in these works, foreign authors do not detail the consumption of fixed doses of antihypertensive combined medicines by the number of active ingredients and their doses. According to the results of our research, it was established that in Ukraine, combinations of iACE and diuretics, and ARB and diuretics occupy leading positions in the structure of consumption. The presented results of the research allow to detail the structure of consumption of combined medicines for AH, consider-

ing the number of active ingredients and their doses in Ukraine in the dynamics of the years.

According to the median share of consumption, the following fixed doses of captopril/HCTD combinations (50 mg/25 mg) – 29.35 %; enalapril/HCTD (10 mg/25 mg) 15.89 %; lisinopril/ HCTD (10 mg/12.5 mg) 14.28 % between iACE and diuretic combinations; valsartan/HCTD (160 mg/12.5 mg (40.65 %); and 80 mg/12.5 mg (26.24 %); losartan/HCTD (50 mg/12.5 mg) 18.55 % among ARB and diuretic combinations, lisinopril/amlodipine (10 mg/5 mg) 36.6 %, perindopril arginine and amlodipine (5 mg/5 mg) 13.77 %, and (10 mg/10 mg) 8.61 % with of all iACE and CCB combinations, as well as valsartan/amlodipine, in all three available doses (160 mg/5 mg, 80 mg/5 mg and 160 mg/10 mg) 46.39 %, 32.01 % and 19.88 %, respectively, among combinations of ARBs and CCBs had the highest median rates of consumption in each respective combination medicine group. Taking this into account, we propose to use the obtained results of the analysis of the structure of consumption of combined AH drugs in the next planning and execution of clinical and economic studies in the context of discussing the issue of expanding the list of combined drugs for the treatment of AH that are subject to reimbursement in Ukraine. Nevertheless, for the further development of effective management decisions on the national level update of the list of drugs subject to reimbursement, an appropriate discussion among clinical and scientific experts on the treatment of AH is needed, which should be based on the results of further pharmacoeconomic studies.

Study limitations. The research used data on retail sales of pharmaceuticals on the territory of Ukraine, except for the temporarily occupied territories of Donetsk, Luhansk Oblasts, and AR Crimea, for a relatively short period of time – 3 years. This did not make it possible to obtain a complete statistical base that could be used in the analysis of the structure of consumption on the scale of the entire country. This statement seems particularly important given the fact that by 2014, these regions had some of the highest rates of medicines consumption in Ukraine as a whole. In addition, the data of only one information base was used, which can also have an impact on the obtained results.

Prospects for further research. Taking into account the implementation of the state program “Afford-

able Medicines”, as well as the presence on the market of Ukraine of mono-component drugs and three-component combined medicines for the treatment of AH, the study of the structure of consumption, its dynamics and the distribution of consumption shares over a longer period of time, namely 5 years, and assessments of their pharmacoeconomic impact are promising.

6. Conclusions

The results of the analysis of retail sales showed that the combined medicines of iACE and diuretics are the most consumed among all two-component combined pharmaceuticals for the treatment of AH in Ukraine in 2018–2020. Further analysis of the structure of consumption of fixed doses of combinations, considering the active substances and their doses, made it possible to identify peculiarities in the formation of the specified indicator. The combination of captopril, enalapril, lisinopril, and valsartan with HCTD, as well as the combination of lisinopril, perindopril arginine, and valsartan with amlodipine, identified in the pattern of consumption, had the highest values of the median share of consumption over three years.

Combinations are proposed to be recommended for conducting clinical and economic studies on their use in the context of discussing the issue of expanding the list of medicines for the treatment of AH with combined pharmaceuticals, which are subject to reimbursement in Ukraine.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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