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RESEARCH ON THE CONSUMPTION OF TWO-COMPONENT FIXED COMBINATIONS OF MEDICINES FOR THE TREATMENT OF ARTERIAL HYPERTENSION IN UKRAINE IN THE PERIOD FROM 2020–2023 AND THE USE OF THE RESULTS IN THE CONTEXT OF OPTIMIZATION OF PHARMACEUTICAL ASSISTANCE AND THE PROSPECTS OF THEIR INCLUSION IN STATE REIMBURSEMENT PROGRAMS

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The aim *to conduct a retrospective study of the consumption of 4 groups of two-component combined drugs for the treatment of arterial hypertension and to determine the structure of their consumption by the number of tablets, , taking into account active substances and their doses, to further formulate proposals to improve the provision of medicines to consumers, in particular through the state reimbursement program "Affordable Medicines".*

Materials and methods: *The objects of the study were retail sales data for the period 2020–2024 on the pharmaceutical market of Ukraine for four groups of combined antihypertensive drugs. The data was provided by the Ukrainian pharmaceutical market research system «Pharmstandard» of the Morion company. The study used statistical and mathematical methods, as well as content analysis, comparative, logical, and systemic analysis, and data generalization.*

Results: *showed that combined drugs of ACE inhibitors and diuretics are the most consumed among all two-component combined drugs for the treatment of hypertension in Ukraine in 2020–2023. By median share of consumption, the following fixed-dose combinations of captopril/HCTZ (50 mg/25 mg) median 29.04%; enalapril/HCTZ (10 mg/25 mg) median 11.74%; lisinopril/HCTZ (10 mg/12.5 mg) median 11.64% and perindopril tertbutylamine with indapamide (8 mg/2.5 mg) – 11.42% among ACE inhibitors and diuretics combinations; valsartan/HCTZ (160 mg/12.5 mg (median 40.02%); and 80 mg/12.5 mg (median 29.07%); losartan/HCTZ (50 mg/12.5 mg) median 11.30% among ARB and diuretic combinations; lisinopril/amlodipine (5 mg/5 mg) median 15.25%; and (10 mg/5 mg) median 11.98% perindopril arginine and amlodipine (5 mg/5 mg) median 13.77%; and perindopril tertbutylamine and amlodipine (4 mg/5 mg) median 11.08%; of all combinations of ACE inhibitors and CCBs; and valsartan/amlodipine, in all three available doses (160 mg/5 mg, 80 mg/5 mg and 160 mg/10 mg) median 43.71%; 31.36% and 20.32% respectively, among the combinations of ARBs and CCBs had the highest median consumption share in each respective group of combination drugs and were used by patients for the treatment of hypertension in Ukraine in 2020–2024.*

Conclusion: *Retail sales results showed that combined drugs of ACE inhibitors and diuretics, as well as combined drugs of ARBs and diuretics, are the most consumed among all two-component combined drugs for the treatment of hypertension in Ukraine in 2020–2023. Further analysis of the structure of consumption of fixed-dose combinations, considering active substances and their doses, made it possible to determine within each study group those fixed doses that have the highest median consumption share values over four years.*

It is regarding them that we propose conducting further clinical and economic studies on their use in the context of discussing the issue of expanding the list of combined drugs for the treatment of hypertension that are subject to reimbursement in Ukraine

Keywords*: arterial hypertension, marketing and pharmacoeconomic research, optimization of pharmaceutical care, rational use of medicines, socio-economic accessibility, adherence to treatment*

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1. Introduction

Statistics from 2019 indicate that there are more than one billion people in the world with a diagnosis of arterial hypertension (AH). Compared with statistics from 1990, the number of such people has doubled. [1] AH is one of the key factors in the development of cardiovascular diseases (CVD), and is responsible for 55% of deaths caused by ischemic heart disease and 45% of deaths resulting from cerebrovascular diseases. However, it is worth emphasizing that AH is a factor for which it is possible to apply preventive measures, including medication. [2] The constant physical and socio-economic accessibility of medicines is a critically important factor for the treatment, control, and prevention of CVD, because

this spectrum of diseases requires long-term treatment. The effectiveness of drugs that lower and control blood pressure (BP) in preventing the development of CVD has been scientifically and practically substantiated and proven. However, as of today, the level of use, and accordingly the consumption of these drugs among the population, is low. As a result, this leads to sub-optimal control of BP in the general population of different countries [3, 4]. In general, to achieve target BP levels, from 50 to 70% of patients require the appointment of two or more antihypertensive drugs [5]. However, it is the number of tablets prescribed to the patient that negatively affects the degree of implementation of the AH treatment strategy, as a result of which low patient adherence to the treatment and prevention of CVD is recorded [6]. Poor compliance to therapy is approximately 10% when a patient is prescribed 1 tablet, increases to 20% when 2 tablets are used, increases to 40% if a patient is prescribed a treatment consisting of 3 tablets, and increases significantly, to almost complete non-adherence, if the patient is forced to adhere to a therapy regimen consisting of four or five tablets [7].

For these reasons, in 2018, the European Society of Cardiology and the European Society of Hypertension jointly developed and published a joint clinical guideline on the treatment of AH, which encouraged the use of combination therapy in most patients, especially in the context of increasing the chances of achieving goals such as lowering BP to target levels and increasing long-term adherence to treatment by reducing the number of tablets, so the emphasis was placed on the use of fixed combinations. The basic drug treatment strategy that was provided for in this clinical guideline involved the use of a dual combination of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) with calcium channel blockers (CCBs) or diuretics as initial therapy for uncomplicated AH [8]. Subsequently, in 2023, the European Society of Hypertension published an updated clinical guideline, which formulated the same approach, but detailed that after starting dual combination therapy, it is important to increase the dosage of the dual combination during further patient management to one that is well tolerated by the patient, and only then switch to the triple combination [9]. In turn, in 2024, the European Society of Cardiology published its clinical guideline on the management of hypertension, which proposed a different strategy: after initiating a dual combination in low therapeutic doses for the treatment of uncomplicated hypertension, if the target blood pressure is not achieved, it is immediately proposed to transfer the patient to a triple combination in low therapeutic doses, with a subsequent increase in the triple combination to those dosages that are well tolerated by the patient and allow achieving target blood pressure levels [10]. According to the current legislation of Ukraine, all these clinical guidelines are permitted for use in medical practice [11].

In Ukraine, CVD and its complications account for 64.3% of all major causes of death in the adult population [12], so for public health authorities, especially in developing countries, increasing the availability of drugs used to treat such socially important diseases as hypertension is a priority [13]. For Ukraine, which is a low- and middle-income country, high prices and low availability are the main barriers that prevent increased use and adherence to essential drugs used in the treatment of CVD, including hypertension [14, 15].

In 2017, the government of Ukraine launched the "Affordable Medicines" state program. The goal of the program is to achieve affordable, equitable, and permanent access to medicines. At the beginning of the program, it covered medicines for the treatment of CVD, type 2 diabetes, and bronchial asthma [16, 17].

According to the National Health Service of Ukraine, since 2020, 9.2 million prescriptions for medicines for the treatment of CVD have been written under the "Affordable Medicines" program. In 2021, the number of prescriptions increased by 20.6% compared to the previous year – 11.1 million prescriptions. In 2022, this figure increased to 12.4 million prescriptions, which is 11.7% more than in 2021, and in 2023 to 13.7 million prescriptions, which is 10.5% more than in the previous year. ACE inhibitors together with diuretics, and beta-blockers with calcium antagonists in the form of non-fixed combinations are most often prescribed within the framework of the "Affordable Medicines" program; their share of the total number of prescriptions issued under the program is 65%. These indicators are one of the evidence of increasing patients' access to drugs for the treatment of CVD, which is an important step by the state in achieving a reduction in CVD mortality in the long term [18].

Later, as the program developed and expanded, it began to cover other nosologies. The concept of the Model List of main medicines, which was introduced by the WHO, was used in the development of this program to meet WHO requirements for the availability of drugs for the treatment of hypertension and other CVDs [19, 20]. In 2019, the WHO Model List of ACE inhibitors was supplemented with 4 combination drugs for the treatment of hypertension – 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, taking into account the active ingredients and doses, makes 12 combinations [21]. In 2024, in accordance with the Resolution of the Cabinet of Ministers of Ukraine No. 773 of June 21, 2024, the following combinations were included in the National List of main drugs of Ukraine: 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) [22]. No explanations were published by the Cabinet of Ministers or the Ministry of Health of Ukraine as to why lisinopril/amlodipine (10 mg/5 mg, 20 mg/5 mg, 20 mg/10 mg) was not included in the National List of PPE. According to the Resolution of the Cabinet of Ministers of Ukraine No. 1380 of December 3, 2024, it is planned to include combined drugs in the reimbursement program

"Affordable Medicines". The list of combined drugs subject to reimbursement corresponds to the list included in the National List of main drugs of Ukraine [23].

Modern European clinical guidelines for the treatment of hypertension [8, 9] provide for the use of combination drugs from the very beginning of treatment, but the range of combination drugs for the treatment of hypertension is significantly larger than the range of combination drugs included in the National List of main drugs [24] and, accordingly, in the "Affordable Medicines" program. Given the specifics of the research methodology that was used when forming a proposal to the WHO to include combination antihypertensive drugs in the WHO Model List [25], in 2022, some authors of this article made a scientific proposal to use a study of the consumption of drugs for the treatment of hypertension as one of the elements for determining those fixed combinations for which it is necessary to initiate questions about their inclusion in the National List of main drugs, and, accordingly, in the "Affordable Medicines" program. However, that publication covered the period from 2018 to 2020 inclusive, which is a rather tangible limitation in terms of time frame, and also did not include all the consequences of the new socio-economic phenomenon at that time, such as quarantine restrictions and the large-scale invasion of the aggressor country.

The new geopolitical, state-legal, and socio-economic realities in which Ukraine found itself create the need to develop tangible, specific, and adapted proposals for combined drugs 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 two-component combined drugs in the form of fixed combinations for the treatment of arterial hypertension and to determine the structure of their consumption by the number of tablets, taking into account the active substances and their doses, for the further formation of proposals for improving the provision of consumers with drugs for the treatment of hypertension, in particular through the state reimbursement program "Affordable Medicines".

2. Research planning (methodology)

To achieve the goal of the study, the following stages of the study were planned:

I – analysis of modern sources of information, which present data on the analysis of the consumption of combined drugs used in the treatment of hypertension in different countries of the world, collection and formation of a statistical base for the study, namely: to analyze the results of retail sales of antihypertensive two-component combined drugs ACEI and diuretics, ACEI and CCBs, ARB and diuretics, ARB and CCBs on the pharmaceutical market of Ukraine in the period from 2020 to 2023 inclusive and to determine the structures of their consumption according to the ATC classification and in accordance with the WHO methodology, by the number of tablets.

II – estimate the consumption of each combined drug in UD, considering the number of active ingredients and their doses in tablets. The current WHO methodology provides for the use of the UD indicator to analyze the structure of consumption of combined antihypertensive drugs, but it considers only the number of tablets, without considering the composition of the combined drug by INN, and doses of active ingredients.

The proposed stage of the study represents an innovative way to obtain a more detailed structure of the consumption of combination drugs for the treatment of hypertension, which, in our opinion, is a logical and consistent addition to the existing WHO methodology [26] on studies of the consumption of combination drugs.

III – to calculate the mass share of consumption of each dose of the combination drug within the study group and its median over four years, and to identify those fixed combinations that had the highest median values of the mass share of consumption over four years.

IV – to calculate the annual growth rate of consumption of each dose of the fixed combination within the study group (ACEI and diuretic; ACEI and CCBs; ARB and diuretic; ARB and CCBs) for each year separately, and the median of the annual growth over four years. Calculate the evolution index for each dose of the combination drug on an annual basis, and the median of the evolution index for each dose of the combination drug over the 4 years studied.

3. Materials and methods

The object of the study was data on retail sales of medicines provided by the market research system "Pharmxplorer" of the company "Proxima Research" [27], in accordance with the approved WHO methodology. The data structuring was built in accordance with the 4th and 5th levels of the ATC classification, and included the following ATC groups: C09BA 01-15, C09BB 02-12, C09DA 01-10, and C09DB01-09. The ATC classification, which is used for drug consumption studies in accordance with the WHO guidelines, involves the use of the daily dose of the drug (DDD), however, in cases where the DDD indicator for many reasons cannot be provided in the form of the number of active ingredients, in particular for combined antihypertensive drugs, the unit dose (UD) indicator is used, which is equal to 1 tablet of a combined drug for the treatment of hypertension. [26] Therefore, sales data were loaded in packages, by stock keeping unit (SKU) for each 5th level of the ATC classification, which details the number of tablets in each package of the drug. The total number of UDs corresponds to the total number of tablets, and for each 5th level of the ATC classification was calculated accordingly, as follows – the number of tablets contained in each SKU multiplied by the number of SKUs.

It is worth noting that the INN of the diuretic, which is part of the combination drugs (C09BA 01-15 and C09DA 01-10), is not indicated in accordance with the WHO Guidelines on the possibilities of using the ATC classification and determining the daily dose of drugs. Also, the methodology for analyzing drug consumption proposed by

the WHO does not consider all variations in the dosages of combination drugs for the treatment of hypertension and counts them as one UD equal to 1 tablet, regardless of the number of active substances and their doses.

Therefore, previously, according to the data of the State Register of Drugs of Ukraine, as of January 1, 2024 [28], the content and doses of active ingredients in each SKU were determined. The obtained data on the number of consumed UDs in each SKU were summarized in accordance with the 5th level of the ATC classification and then structured into study groups in accordance with 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 – ACEI and diuretics, C09BB – ACEI and calcium channel blockers, C09DA – ARB and diuretics, and C09DB – ARB and calcium channel blockers. These four groups of combinations are recommended by modern European clinical guidelines for the treatment of hypertension as a priority for initial and maintenance therapy of hypertension [29]. In the next step, the obtained data were structured, considering the number of active substances (by INN) and their doses within the 4th level of the ATC classification. The share of consumption of the studied dose of a fixed combination of drugs was calculated according to the total number of UD consumed within each studied group, according to the 4th level of the ATC classification, for each year separately. The increase in consumption of each fixed dose of drugs was determined as follows: the difference in the drug consumption indicator (in UD) of the studied year from the indicator of the previous year, divided by the indicator of the previous year, and multiplied by 100%. The index of evolution of consumption of each fixed dose of a combined drug was determined as (1+ increase in consumption of the fixed dose of the drug) divided by (1+ increase in consumption of the entire group to which the combined drug belongs) for a given year. In the further analysis of the drug consumption structure, the median share of consumption of each fixed dose over four years, the median increase in consumption and the median index of consumption evolution were determined, as these indicators provide an opportunity to gain an understanding of the central tendency of the distribution of consumption share data and the dynamics of consumption trends for a certain variable over time [30].

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

4. Research results

The results of data processing on retail sales of antihypertensive two-component combination drugs, according to the 4th level of the ATC classification, on the pharmaceutical market of Ukraine, by UD indicator in the period from 2020 to 2024 showed that the total number of consumed combined ACEI and diuretic drugs was 325,366,459 UD in 2020, 347,501,430 UD in 2021, and 322,275,141 UD in 2022 and 325,328,886 in 2023, respectively. The consumption of combined ACEI and CCBs was 46,763,064, 49,735,678, 46,406,740 and 45,789,288 UD in 2020, 2021, 2022 and 2023, respectively. Regarding combined ARB and diuretics, the number of UD consumed was 96,784,366 in 2020, 103,500,070 in 2021, 97,121,668 in 2022 and 100,810,542 in 2023. And the consumption of combinations of ARBs and CCBs was at 35,509,272 UD in 2020, 42,182,812 UD in 2021, 40,305,042 and 43,435,009 UD in 2022 and 2023, respectively.

These data show that combined ACEI and diuretic drugs were the largest group among two-component combined drugs consumed by Ukrainian patients in the period between 2020 and 2023 inclusive and had a consumption share of 64.50%; 64.01%, 63.68% and 63.13% per year, respectively. Combinations of ARB and diuretics occupy the second position in the consumption share for the corresponding period (19.19%; 19.06%; 19.19% and 19.56% per year, respectively). The consumption share of combinations of ACEI and CCBs was only 9.27%; 9.16%; 9.17% and 8.88% per year. Combinations of ARB and CCBs were the least consumed during this period, having only 7.04%; 7.77%; 7.96% and 8.43% of the consumption share in each year, respectively.

The results of data processing of retail sales of antihypertensive two-component combination drugs, according to the 4th and 5th levels of the ATC classification, on the pharmaceutical market of Ukraine, by UD indicator in the period from 2020 to 2023 are presented in Table 1.

As can be seen from Table 1, among the combinations of ACEI and diuretics, for the period 2020–2022, the most consumed were combinations of diuretics with captopril (32.90% in 2020; 33.10% in 2021 and 33.33% in 2022), however, in 2023, the leaders were combinations of perindopril with diuretics – 36.03%, while the share of consumption of combinations of captopril with diuretics reached only 31.23%. The consumption of combinations of perindopril with diuretics increased every year (23.54% in 2020; 27.50% in 2021 and 31.24% in 2022). The share of consumption of combinations of lisinopril with diuretics was 21.90%; 20.14%; 18.23%; 19.9% in 2020, 2021, 2022 and 2023 respectively, and enalapril – 19.89% in 2020; 17.47% in 2021, 15.65% in 2022 and 14.36% in 2022. However, the consumption of combined drugs lisinopril with diuretics decreased year-on-year, by 1,277,009 UD (–1.79%) in 2021 compared to 2020, by 11,230,499 UD (–19.11%) in 2022 compared to 2021, and by 3,864,046 UD (–7.03%) in 2023 compared to 2022. The same dynamics were observed with the combined drugs enalapril with diuretics, in 2021 by –6.14% compared to 2020, and by 16.92% in 2022 compared to 2021, and in 2023 by 7.98% compared to 2022. At the same time, the consumption of combinations of perindopril with diuretics increased every year, in 2021 by 24.77% compared to the previous year, by 5.34% in 2022 compared to 2021, and by 16.41% in 2023 compared to 2022. The consumption of valsartan and diuretics was the highest among all combined ARBs and diuretics: 67.58% in 2020, 69.35% in 2021, 73.42% and

75.37% in 2022 and 2023, respectively, and increased annually in both the number of tablets and mass share. The consumption of losartan and diuretic combinations decreased annually, in 2021 by 2,639,625 UD (15.58%) compared to the previous year, by 5,938,101 UD in 2022 compared to 2021, and in 2023 by 1,963,563 UD compared to the previous year. The use of other ARB and diuretic combinations, except for losartan and diuretic combinations, mostly showed a trend towards increasing the number of UDs consumed during the studied period. However, based on the available data, it is not possible to clearly understand which type of diuretic by INN was included in these combinations.

Consumption data for ACEI and CCBs combinations show that combinations of lisinopril and perindopril with amlodipine were the most consumed among patients in 2020–2023 in Ukraine. Combinations of valsartan with amlodipine were the most consumed (97.78% in 2020, 96.04% in 2021, 95.35% and 92.33% in 2022 and 2023) among all combinations of ARBs and CCBs consumed in 2020–2023. The dynamics of positive growth is observed among the combinations of enalapril with lercanidipine (169% in 2021, 32.96% and 13.75% in 2020), perindopril and amlodipine (12.50% in 2021 and 2.42% in 2023), and ramipril with amlodipine (6.93% in 2021 and 8.4% in 2023), while for the combinations of lisinopril with amlodipine there is an annual trend of decreasing the number of UD consumed. Among all combined drugs ARBs and CCBs, a trend of annual growth in consumption was recorded during the study period. Therefore, it can be argued that in Ukraine the structure of consumption of combined antihypertensive drugs is dynamic and heterogeneous, with the predominant consumption of combined ACEI and diuretic drugs.

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

The results of consumption of fixed doses of combinations of ACEI and diuretics are presented in Table 2.

The data from Table 2 show that the most consumed were fixed-dose combinations of captopril with hydrochlorothiazide (HCTZ) 50 mg/25 mg, with a median consumption share of 29.04%; enalapril and HCTZ 10 mg/25 mg (11.64%), lisinopril with HCTZ 10 mg/12.5 mg (11.64%) and perindopril with indapamide 8 mg/2.5 mg (11.42%).

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

Table 1

Results of processing and summarizing data on the consumption of antihypertensive two-component combination drugs in Ukraine in 2020–2023, by UD indicator according to the 5th and 4th levels of the ATC classification, according to the WHO methodology

No.	ATC classification level 5 (INN)	UD Consumed per year			
		2020	2021	2022	2023
Consumption structure of combined drugs belonging to level 4 of the ATC classification C09BA (ACEI and diuretics)					
1	Captopril and diuretics C09BA01	107,052,540	115,016,458	107,401,439	101,563,021
2	Enalapril and diuretics C09BA02	64,701,389	60,723,560	50,446,788	46,718,458
3	Lisinopril and diuretics C09BA03	71,263,916	69,986,907	58,756,408	54,892,362
4	Perindopril and diuretics C09BA04	76,592,610	95,563,698	100,668,893	117,186,025
5	Ramipril and hydrochlorothiazide C09BA05	5,239,372	5,713,430	4,825,309	4,898,166
6	Quinapril and diuretics C09BA06	380,160	368,985	135,482	385
7	Fosinopril and diuretics C09BA09	0	0	0	0
8	Zofenopril and diuretics C09BA15	136,472	128,392	40,822	70,469
Consumption structure of combined drugs belonging to level 4 of the ATC classification C09BB (ACEIs and CCBs)					
1	Enalapril and lercanidipine C09BB02	420,028	1,130,018	1,685,759	1,954,699
2	Lisinopril and amlodipine C09BB03	18,473,730	18,091,903	14,805,565	12,975,711
3	Perindopril and amlodipine C09BB04	22,391,490	25,190,030	24,744,121	25,342,754
4	Enalapril and nitrendipine C09BB06	899,250	427,875	455,076	403,534
5	Ramipril and almodipine C09BB07	4,578,566	4,895,852	4,716,219	5,112,590
Consumption structure of combined drugs belonging to level 4 of the ATC classification C09DA (ARB and diuretics)					
1	Losartan and diuretics C09DA01	19,573,420	16,933,795	10,995,694	9,032,131
2	Valsartan and diuretics C09DA03	65,410,550	71,774,583	71,309,574	75,981,672
3	Irbesartan and diuretics C09DA04	2,529,860	2,797,231	2,493,667	2,722,454
4	Candesartan and diuretics C09DA06	4,265,340	4,740,891	4,689,917	4,837,176
5	Telmisartan and diuretics C09DA07	2,479,372	3,785,752	4,129,666	4,668,213
6	Olmesartan medoxomil and diuretics C09DA08	447,244	640,669	698,735	610,408
7	Azilsartan medoxomil and diuretics C09DA09	2,078,580	2,827,149	2,804,415	2,958,488
Consumption structure of combined drugs that belong to level 4 of the ATC classification C09DB (ARBs and CCBs)					
1	Valsartan and amlodipine C09DB01	34,721,234	40,512,841	38,430,835	40,104,964
2	Olmesartan medoxomil and amlodipine C09DB02	695,128	1,000,534	1,130,704	1,475,599
3	Telmisartan and amlodipine C09DB04	92,910	669,437	743,503	1,854,446

Table 2

Consumption of fixed-dose combinations of ACEIs and diuretics in Ukraine in 2020–2023

No.	AI doses (in mg)	Number of tablets consumed per year, mass share of consumption per year and growth rate of consumption compared to the previous year, in%				Median consumption share over four years, in%
		2020	2021	2022	2023	
C09BA01 Captopril and hydrochlorothiazid						
1	50/12.5	11,920,340 3.66%	14,782,656 4.25%	12,754,778 3.96%	12,456,894 3.83%	3.89%
2	50/25	95,132,200 29.24%	100,233,801 28.84%	94,646,661 29.37%	89,106,127 27.39%	29.04%
C09BA02 Enalapril and hydrochlorothiazide						
3	5/12.5	260 0.00%	0 0.00%	83 0.00%	0 0.00%	0.00%
4	10/12.5	16,332,220 5.02%	15,298,088 4.40%	12,566,820 3.90%	11,893,390 3.66%	4.15%
5	10/25	45,438,530 13.97%	42,715,516 12.29%	36,058,064 11.19%	33,429,444 10.28%	11.74%
6	20/12.5	2,594,904 0.80%	2,095,625 0.60%	1,621,871 0.50%	1,395,123 0.43%	0.55%
C09BA02 Enalapril and indapamide						
7	10/2.5	138,780 0.04%	225895.95 0.07%	68760 0.02%	501 0.00%	0.03%
8	20/2.5	196,695 0.06%	388,436 0.11%	131,190 0.04%	0 0.00%	0.05%
C09BA03 Lisinopril and hydrochlorothiazide						
9	10/12.5	44,295,528 13.61%	43,246,339 12.44%	34,950,147 10.84%	32,717,995 10.06%	11.64%
10	20/12.5	26,968,388 8.29%	26,740,568 7.70%	23,806,261 7.39%	22,174,367 6.82%	7.54%
C09BA04 Perindopril tert-butylamine and indapamide						
11	2/0.625	1,045,680 0.32%	1,527,100 0.44%	1,965,806 0.61%	2,143,245 0.66%	0.52%
12	4/1.25	16,839,420 5.18%	22,686,485 6.53%	25,464,999 7.90%	31,036,437 9.54%	7.22%
13	8/2.5	28,076,160 8.63%	36,678,992 10.56%	39,605,505 12.29%	47,043,938 14.46%	11.42%
C09BA04 Perindopril arginine and indapamide						
14	2.5/0.625	6,692,190 2.06%	7018875.3 2.02%	6775281 2.10%	8243262.9 2.53%	2.08%
15	5/1.25	13,289,370 4.08%	15,538,868 4.47%	14,500,684 4.50%	14,348,515 4.41%	4.44%
16	10/2.5	10,649,790 3.27%	12,113,378 3.49%	12,356,618 3.83%	14,370,628 4.42%	3.66%
C09 BA05 Ramipril and hydrochlorothiazide						
17	2.5/12.5	293,262 0.09%	231,130 0.07%	137,158 0.04%	98,616 0.03%	0.05%
18	5/12.5	1,180,672 0.36%	1,358,907 0.39%	1,287,591 0.40%	1,452,868 0.45%	0.40%
19	5/25	2,916,092 0.90%	3,134,022 0.90%	2,352,101 0.73%	2,158,286 0.66%	0.81%
20	10/12.5	848,446 0.26%	988,987 0.28%	1,048,192 0.33%	1,188,039 0.37%	0.30%
21	10/25	900 0.01%	384 0.00%	267 0.00%	357 0.00%	0.00%
C09BA06 Quinapril and hydrochlorothiazide						
22	10/12.5	166,260 0.05%	161,287 0.05%	76,060 0.02%	179 0.00%	0.04%
23	20/12.5	213,900 0.07%	207,698 0.06%	59,422 0.02%	206 0.00%	0.04%
C09BA09 Fosinopril and hydrochlorothiazide						
24	20/12.5	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0.00%
25	30/12.5	136,472 0.04%	128,392 0.04%	40,822 0.01%	70,469 0.02%	0.03%

Table 3

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

No.	AI doses (in mg)	Number of tablets consumed per year, considering the number of active substances and doses, mass share of consumption per year and consumption growth rate, in%				Median consumption share over four years, in%
		2020	2021	2022	2023	
C09DA01 Losartan and hydrochlorothiazide						
1	50/12.5	17,804,280 18.40%	14,247,250 13.77%	8,585,421 8.84%	6,915,884 6.86%	11.30%
2	100/12.5	842,010 0.87%	885,796 0.86%	1,497,756 1.54%	1,462,650 1.45%	1.16%
3	100/25	927,130 0.96%	1,800,749 1.74%	912,517 0.94%	653,597 0.65%	0.95%
C09DA03 Valsartan and hydrochlorothiazide						
4	80/12.5	25,399,282 26.24%	28,728,369 27.76%	29,514,966 30.39%	31,796,432 31.54%	29.07%
5	160/12.5	38,055,438 39.32%	40,823,536 39.44%	39,428,394 40.60%	41,542,594 41.21%	40.02%
6	160/25	1,387,486 1.43%	1,663,302 1.61%	1,845,059 1.90%	2,170,136 2.15%	1.75%
7	320/12.5	368,882 0.38%	355,417 0.34%	334,488 0.34%	298,926 0.30%	0.34%
8	320/25	199,462 0.21%	203,959 0.20%	186,667 0.19%	173,584 0.17%	0.19%
C09DA04 Irbesartan and hydrochlorothiazide						
9	150/12.5	1,292,006 1.33%	1,509,261 1.46%	1,340,300 1.38%	1,524,873 1.51%	1.42%
10	300/12.5	1,237,854 1.28%	1,287,970 1.24%	1,153,367 1.19%	1,197,581 1.19%	1.22%
C09DA06 Candesartan and hydrochlorothiazide						
11	16/12.5	2,362,920 2.44%	2,579,628 2.49%	2,589,947 2.67%	2,863,230 2.84%	2.58%
12	32/25	1,902,420 1.97%	2,161,263 2.09%	2,099,970 2.16%	1,973,946 1.96%	2.03%
C09DA07 Telmisartan and hydrochlorothiazide						
13	40/12.5	477,596 0.49%	1,047,612 1.01%	1,140,167 1.17%	1,424,428 1.41%	1.09%
14	80/12.5	1,786,792 1.85%	2,378,697 2.30%	2,601,192 2.68%	2,715,775 2.69%	2.49%
15	80/25	214,984 0.22%	35,9443 0.35%	388,307 0.40%	528,010 0.52%	0.37%
C09DA08 Olmesartan medoxomil and hydrochlorothiazide						
16	20/12.5	354,256 0.37%	492,427 0.48%	536,866 0.55%	440,576 0.44%	0.46%
17	20/25	84,980 0.09%	84,111 0.08%	83,650 0.09%	120,840 0.12%	0.09%
18	40/12.5	8,008 0.01%	64,131 0.06%	78,219 0.08%	48,992 0.05%	0.06%
C09DA09 Azilsartan medoxomil and hydrochlorothiazide						
19	40/12.5	1,370,908 1.42%	1,881,244 1.82%	1,776,895 1.83%	1,996,482 1.98%	1.82%
20	40/25	707,672 0.73%	945,905 0.91%	1,027,520 1.06%	962,006 0.95%	0.93%

According to the data presented in Table 3, we can state that the combination of valsartan and HCTZ 160 mg/12.5 mg occupied the largest share of consumption during all four years studied – 39.32%; 39.44%; 40.60% and 41.21%, among all fixed-dose combinations of ARBs and diuretics. The combination of valsartan with HCTZ in a dosage of 80 mg/12.5 mg was the second most consumed in the group of ARBs and diuretics (26.24%; 27.76%; 30.39% and 31.54%, respectively, in 2020, 2021, 2022, 2023). The third was a fixed dose combination of losartan with HCTZ 50 mg /12.5 mg, with a consumption share of (18.40%; 13.77%; 8.84% and 6.86% in 2020, 2021, 2022 and 2023, respectively).

Continuing the second phase of the study, the consumption of fixed dose combinations of ACEI and CCBs, as well as combinations of ARB and CCBs, was assessed, and the results are presented in Table 4 and Table 5, respectively.

Table 4

Consumption of fixed-dose combinations of ACEIs and CCBs in Ukraine in 2020–2023

No.	AI doses (in mg)	Number of tablets consumed per year, considering the number of active substances and doses, mass share of consumption per year and consumption growth rate, in%				Median consumption shares over four years, in%
		2020	2021	2022	2023	
C09BB02 Enalapril and lercanidipine						
1	10/10	208,852 0.45%	676,046 1.36%	1,034,554 2.23%	1,183,461 2.58%	1.79%
2	20/10	211,176 0.45%	453,972 0.91%	651,205 1.40%	771,181 1.68%	1.16%
3	20/20	0 0.00%	0 0.00%	0 0.00%	57 0.00%	0.00%
C09BB03 Lisinopril and amlodipine						
4	5/5	255,960 0.55%	9,302,873 18.70%	7,440,492 16.03%	6,624,345 14.47%	15.25%
5	10/5	16,066,650 34.36%	6,338,800 12.74%	5,205,202 11.22%	4,622,414 10.09%	11.98%
6	20/5	314,370 0.67%	321,061 0.65%	233,880 0.50%	162,502 0.35%	0.57%
7	20/10	1,836,750 3.93%	2,129,169 4.28%	1,925,991 4.15%	1,566,450 3.42%	4.04%
C09BB04 Perindopril arginine and amlodipine						
8	3.5/2.5	150 0.00%	0 0.00%	0 0.00%	0 0.00%	0.00%
9	5/5	6,647,220 14.21%	6,989,484 14.05%	6,260,917 13.49%	5,895,650 12.88%	13.77%
10	7/5	180 0.00%	0 0.00%	0 0.00%	0 0.00%	0.00%
11	5/10	1,158,960 2.48%	1,156,356 2.33%	1,121,494 2.42%	1,094,145 2.39%	2.40%
12	10/5	2,783,700 5.95%	2,839,612 5.71%	2,625,338 5.66%	3,404,418 7.43%	5.83%
13	10/10	3,753,510 8.03%	3,685,122 7.41%	3,335,073 7.19%	2,671,421 5.83%	7.30%
14	14/10	270 0.00%	0 0.00%	0 0.00%	0 0.00%	0.00%
C09BB04 Perindopril tert-butylamine and amlodipine						
15	4/5	3,624,960 7.75%	5,095,838 10.25%	5,528,836 11.91%	6,472,286 14.13%	11.08%
16	4/10	332,010 0.71%	365,918 0.74%	413,700 0.89%	369,354 0.81%	0.77%
17	8/5	1,615,530 3.45%	1,833,047 3.69%	1,994,648 4.30%	1,985,368 4.34%	3.99%
18	8/10	2,475,000 5.29%	3,224,653 6.48%	3,464,115 7.46%	3,450,112 7.53%	6.97%
C09BB06 Enalapril and nitrendipine						
19	10/20	899,250 1.92%	427,875 0.86%	455,076 0.98%	403,534 0.88%	0.93%
C09BB07 Ramipril and almodipine						
20	5/5	2,466,480 5.27%	2,675,654 5.38%	2,619,386 5.64%	2,908,137 6.35%	5.51%
21	5/10	390,314 0.83%	347,357 0.70%	330,481 0.71%	359,071 0.78%	0.75%
22	10/5	1,256,360 2.69%	1,306,551 2.63%	1,232,401 2.66%	1,246,052 2.72%	2.67%
23	10/10	465,412 1.00%	566,290 1.14%	533,951 1.15%	599,330 1.31%	1.14%

As can be seen from Table 4, in 2020, the largest share of consumption among ACEI and CCB combinations belonged to the fixed combination of lisinopril with amlodipine at a dosage of 10 mg/5 mg – 34.36%, and from 2021 to 2023, to the fixed dose combination of lisinopril with amlodipine 5 mg/5 mg – 18.7% in 2021, 16.03% and 14.47% in 2022 and 2023, respectively. The second place in terms of consumption share is occupied

by the fixed dose combination of perindopril arginine and amlodipine 5 mg/5 mg, occupying more than 10% each year. At the same time, the combination of lisinopril with amlodipine at a dosage of 10 mg/5 mg in 2020 ranked first with a mass share of consumption of 34.36%, but in the following three years they significantly decreased to 12.74% in 2021, 11.22% in 2022 and 10.09% in 2023. In addition, the combination of perindopril tertbutylamine with indapamide at a dosage of 4 mg/5 mg demonstrated an annual increase in the mass share of consumption in the ACEI and CCBs group – from 7.75% in 2020 to 14.13% in 2023. Among all consumed combinations of ARBs and CCBs, the combination of valsartan and amlodipine at a dosage of 160 mg/5 mg accounts for more than 40% each year, and the fixed dose combination of valsartan/amlodipine 80 mg/5 mg accounts for more than 30% of the consumption each year, and at a dosage of 160 mg/5 mg – more than 20% annually.

The next stage of the study was to calculate the growth rates of consumption of combined drugs for each fixed dose and calculate their consumption evolution index on an annual basis. The results of the calculations are presented in Tables 6–9.

From the data in Table 6, we can conclude that during the four years studied, the combinations of perindopril tertbutylamine in dosages of 4 mg/1.25 mg; 2 mg/0.625 mg and 8 mg/2.5 mg demonstrated the highest median increase rates (26.25%; 24.81%; and 22.74%) for the specified period, as well as the combination of perindopril arginine in dosage 10 mg/2.5 mg – 12.27%. However, if we analyze the median of the consumption evolution index, the fixed combination of perindopril tertbutylamine 2 mg/0.625 mg demonstrated a higher median – 130, while the dosage of 4 mg/1.25 mg – 124, despite the highest median of consumption increase.

From the analysis of Table 8, we can state that the highest median consumption growth rates were demonstrated by the combinations of telmisartan with HCTZ in dosages of 40 mg/12.5 mg – 72.14%; and 80 mg/25 mg – 51.59%, and the highest median consumption evolution index rates were 163 and 144; and the dosage of 80/12.5 mg – only 21.24% with a median evolution index of 121. It is also worth emphasizing that the combination of olmesartan with HCTZ in all fixed dosages demonstrated a median consumption growth rate above 20% over the studied period – 20/12.5 mg – 24.01%; dosage of 40/12.5 mg – 21.97%; and dosage of 20/25 mg – 21.96%.

According to the results of the analysis of the data presented in Table 8, it can be stated that the combination of enalapril with lercanidipine in dosages of 10/10 mg and 20/10 mg demonstrated the highest median increase in consumption – 23.62% and 22.92%; as well as the highest median evolution index – 130 and 129, respectively. In addition, the combination of perindopril tert-butylamine with amlodipine in dosage 4/5 mg had a median increase in consumption of 20.3% over the 4 years studied, and an evolution index of 123; and the same combination in the dosage of 8/5 mg – 10.78% and the median evolution index – 112.

According to the data presented in Table 9, we can conclude that fixed-dose combinations of telmisartan with amlodipine demonstrated the highest median consumption increase and evolution index – 40/5 mg – 255.63% and 302; 80/10 mg – 201.28% and 280; and 80/5 mg – 98.11% and 184.

Table 5

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

No.	AI doses (in mg	Number of tablets consumed per year, considering the number of active ingredients and doses, mass share of consumption per year and rate of consumption growth, in%				Median consumption share over three years, in%
		2020	2021	2022	2023	
C09DB01 Valsartan and amlodipine						
1	80/5	11,155,176 31.41%	13,229,150 31.36%	12,642,572 31.37%	13,472,546 31.02%	31.36%
2	160/5	16,508,012 46.49%	18,722,764 44.38%	17,344,841 43.03%	17,799,305 40.98%	43.71%
3	160/10	7,058,046 19.88%	8,560,927 20.29%	8,443,422 20.95%	8,833,113 20.34%	20.32%
C09DB02 Olmesartan medoxomil and amlodipine						
4	20/5	382,200 1.08%	490,253 1.16%	530,615 1.32%	688,374 1.58%	1.24%
5	40/10	312,928 0.88%	510,281 1.21%	600,089 1.49%	787,225 1.81%	1.35%
C09DB04 Telmisartan and amlodipine						
6	40/5	30,210 0.09%	205,415 0.49%	185,835 0.46%	605,142 1.39%	0.47%
7	40/10	0 0.00%	0 0.00%	5036 0.01%	11,526 0.03%	0.01%
8	80/5	38,700 0.11%	315,633 0.75%	414,062 1.03%	820,293 1.89%	0.89%
9	80/10	24,000 0.07%	148,389 0.35%	138,570 0.34%	417,485 0.96%	0.35%

Table 6

Growth rates and evolution index of consumption of fixed doses of combinations of ACEI and diuretics in Ukraine in 2020–2023

No.	AI doses (in mg)	Consumption growth rate compared to the previous year and consumption evolution index, in%				Medians of indicators
		2020	2021	2022	2023	
C09BA01 Captopril and hydrochlorothiazid						
1	50/12.5	7.81% 111	24.01% 116	–13.72% 93	–2.34% 97	2.74% 104
2	50/25	–3.03% 100	5.36% 99	–5.57% 102	–5.85% 93	–4.30% 99
C09BA02 Enalapril and hydrochlorothiazide						
3	5/12.5	1,200.00% 1336	–100.00% 0	0% 108	–100.00% 0	–100.00% 54
4	10/12.5	–15.71% 87	–6.33% 88	–17.85% 89	–5.36% 94	–11.02% 88
5	10/25	–14.43% 88	–5.99% 88	–15.59% 91	–7.29% 92	–10.86% 90
6	20/12.5	–10.31% 92	–19.24% 76	–22.61% 83	–13.98% 85	–16.61% 84
C09BA02 Enalapril and indapamide						
7	10/2.5	–72.77% 28	62.77% 152	–69.56% 33	–99.27% 1	–71.17% 30
8	20/2.5	–81.94% 19	97.48% 185	–66.23% 36	–100.00% 0	–74.08% 27
C09BA03 Lisinopril and hydrochlorothiazide						
9	10/12.5	–7.20% 95	–2.37% 91	–19.18% 87	–6.39% 93	–6.79% 92
10	20/12.5	–6.35% 96	–0.84% 93	–10.97% 96	–6.85% 92	–6.60% 94
C09BA04 Perindopril tert-butylamine and indapamide						
11	2/0.625	20.89% 124	46.04% 137	28.73% 139	9.03% 108	24.81% 130
12	4/1.25	30.63% 134	34.72% 126	12.25% 121	21.88% 121	26.25% 124
13	8/2.5	26.69% 30	30.64% 122	7.98% 116	18.78% 118	22.74% 120
C09BA04 Perindopril arginine and indapamide						
14		7.29% 110	4.88% 98	–3.47% 104	21.67% 121	6.08% 107
15	5/1.25	–4.59% 98	16.93% 109	–6.68% 101	–1.05% 98	–2.82% 99
16	10/2.5	10.79% 114	13.74% 106	2.01% 110	16.30% 115	12.27% 12
C09BA05 Ramipril and hydrochlorothiazide						
17	2.5/12.5	–19.50% 83	–21.19% 74	–40.66% 64	–28.10% 71	–24.64% 73
18	5/12.5	7.22% 110	15.10% 108	–5.25% 102	12.84% 112	10.03% 109
19	5/25	0.70% 103	7.47% 101	–24.95% 81	–8.24% 91	–3.77% 96
20	10/12.5	–11.12% 91	16.56% 109	5.99% 114	13.34% 112	9.66% 111
21	10/25	–21.05% 81	–57.33% 40	–30.47% 75	33.71% 132	–25.76% 78
C09BA06 Quinapril and hydrochlorothiazide						
22	10/12.5	–22.30% 80	–2.99% 91	–52.84% 51	–99.76% 0	–37.57% 65
23	20/12.5	–10.31% 92	–2.90% 91	–71.39% 31	–99.65% 0	–40.85% 61
C09BA09 Fosinopril and hydrochlorothiazide						
24	20/12.5	–100.00% 0	N/A 94	N/A N/A	N/A N/A	–100.00% 47
25	30/12.5	18.70% 122	–5.92% 88	–68.21% 34	72.63% 171	6.39% 105

Table 7

Growth rates and evolution index of consumption of fixed-dose combinations of ARBs and diuretics in Ukraine in 2020–2023

No.	AI doses (in mg)	Consumption growth rate compared to the previous year and consumption evolution index, in%				Medians of indicators
		2020	2021	2022	2023	
C09DA01 Losartan and hydrochlorothiazide						
1	50/12.5	–1.26% 98	–19.98% 75	–39.74% 64	–19.45% 78	–19.71% 76
2	100/12.5	–15.55% 83	5.20% 98	69.09% 180	–2.34% 94	1.43% 96
3	100/25	–69.25% 30	94.23% 182	–49.33% 54	–28.37% 69	–38.85% 62
C09DA03 Valsartan and hydrochlorothiazide						
4	80/12.5	7.50% 106	13.11% 106	2.74% 109	7.73% 104	7.61% 106
5	160/12.5	–2.30% 96	7.27% 100	–3.42% 103	5.36% 102	1.53% 101
6	160/25	7.62% 106	19.88% 112	10.93% 118	17.62% 113	14.27% 113
7	320/12.5	–4.61% 94	–3.65% 90	–5.89% 100	–10.63% 86	–5.25% 92
8	320/25	–4.56% 94	2.25% 96	–8.48% 98	–7.01% 90	–5.78% 95
C09DA04 Irbesartan and hydrochlorothiazide						
9	150/12.5	21.92% 120	16.82% 109	–11.19% 95	13.77% 110	15.29% 109
10	300/12.5	–5.27% 94	4.05% 97	–10.45% 95	3.83% 100	–0.72% 96
C09DA06 Candesartan and hydrochlorothiazide						
11	16/12.5	2.31% 101	9.17% 102	0.40% 107	10.55% 107	5.74% 104
12	32/25	13.45% 112	13.61% 106	–2.84% 104	–6.00% 91	5.31% 105
C09DA07 Telmisartan and hydrochlorothiazide						
13	40/12.5	206.81% 303	119.35% 205	8.83% 116	24.93% 120	72.14% 163
14	80/12.5	114.11% 211	33.13% 124	9.35% 117	4.41% 101	21.24% 121
15	80/25	157.91% 255	67.20% 156	8.03% 115	35.98% 131	51.59% 144
C09DA08 Olmesartan medoxomil and hydrochlorothiazide						
16	20/12.5	51.79% 150	39.00% 130	9.02% 116	–17.94% 79	24.01% 123
17	20/25	71.08% 169	–1.02% 93	–0.55% 106	44.46% 139	21.96% 123
18	40/12.5	N/A N/A	700.84% 749	21.97% 130	–37.37% 60	21.97% 130
C09DA09 Azilsartan medoxomil and hydrochlorothiazide						
19	40/12.5	92.42% 190	37.23% 128	–5.55% 101	12.36% 108	24.79% 118
20	40/25	7.90% 107	33.66% 125	8.63% 116	–6.38% 90	8.27% 111

Table 8

Growth rates and evolution index of consumption of fixed-dose combinations of ACEIs and CCBs in Ukraine in 2020–2023

No.	AI doses (in mg)	Consumption growth rate compared to the previous year and consumption evolution index, in%				Medians of indicators
		2020	2021	2022	2023	
1	2	3	4	5	6	7
C09BB02 Enalapril and lercanidipine						
1	10/10	–1.49% 102	223.70% 305	34.65% 145	12.58% 114	23.62% 130
2	20/10	6.03% 110	114.97% 203	30.29% 140	15.56% 117	22.92% 129

Continuation of Table 8

1	2	3	4	5	6	7
3	20/20	N/A N/A	0% 94	0% 108	100.00% 203	100.00% 108
C09BB03 Lisinopril and amlodipine						
4	5/5	–36.80% 65	3534.50% 3430	–25.03% 81	–12.32% 89	–18.68% 85
5	10/5	–9.17% 94	–60.55% 37	–21.78% 84	–12.61% 89	–17.19% 86
6	20/5	–26.94% 76	2.13% 96	–37.28% 68	–43.92% 57	–32.11% 72
7	20/10	5.79% 109	15.92% 109	–10.55% 96	–22.95% 78	–2.38% 103
C09BB04 Perindopril arginine and amlodipine						
8	5/5	–0.13% 103	5.15% 99	–11.64% 95	–6.20% 95	–3.16% 97
9	5/10	–4.64% 99	–0.22% 94	–3.11% 104	–2.50% 99	–2.80% 99
10	10/5	–0.02% 103	2.01% 96	–8.16% 99	22.88% 125	0.99% 101
11	10/10	–9.78% 93	–1.82% 93	–10.50% 96	–24.84% 76	–10.14% 93
C09BB04 Perindopril tert-butylamine and amlodipine						
12	4/5	26.03% 130	40.58% 133	7.83% 116	14.58% 116	20.30% 123
13	4/10	1.43% 105	10.21% 104	11.55% 120	–12.01% 89	5.82% 104
14	8/5	16.16% 120	13.46% 107	8.10% 116	–0.47% 101	10.78% 112
15	8/10	10.74% 115	30.29% 123	6.91% 115	–0.41% 101	8.83% 115
C09BB06 Enalapril and nitrendipine						
16	10/20	–29.09% 73	–52.42% 45	5.98% 114	–12.77% 88	–20.93% 81
C09BB07 Ramipril and almodipine						
17	5/5	9.33% 113	8.48% 102	–2.15% 105	9.93% 111	8.90% 108
18	5/10	–4.56% 99	–11.01% 84	–5.11% 102	7.96% 109	–4.83% 100
19	10/5	–5.95% 97	3.99% 98	–6.02% 101	1.10% 102	–2.43% 100
20	10/10	–8.48% 95	21.67% 115	–6.06% 101	10.91% 112	2.43% 107

Table 9

Growth rates and evolution index of consumption of fixed-dose combinations of ARBs and CCBs in Ukraine in 2020–2023

No.	AI doses (in mg)	Consumption growth rate compared to the previous year and consumption evolution index, in%				Medians of indicators
		2020	2021	2022	2023	
1	2	3	4	5	6	7
C09DB01 Valsartan and amlodipine						
1	80/5	8.52% 98	18.59% 100	–4.43% 100	6.56% 99	7.54% 99
2	160/5	10.80% 100	13.42% 95	–7.36% 97	2.62% 95	6.71% 96
3	160/10	7.13% 97	21.29% 102	–1.37% 103	4.62% 97	5.87% 100
C09DB02 Olmesartan medoxomil and amlodipine						
4	20/5	163.72% 239	28.27% 108	8.23% 113	29.73% 163.72%	29.00% 117
5	40/10	52.22% 138	63.07% 137	17.60% 123	31.18% 52.22%	41.70% 130

Continuation of Table 9

1	2	3	4	5	6	7
C09DB04 Telmisartan and amlodipine						
6	40/5	N/A N/A	579.96% 572	–9.53% 95	225.63% 302	225.63% 302
7	40/10	N/A N/A	N/A N/A	N/A N/A	128.87% 212	
8	80/5	N/A N/A	715.59% 687	31.18% 137	98.11% 184	98.11% 184
9	80/10	N/A N/A	518.29% 520	–6.62% 98	201.28% 280	201.28% 280

5. Discussion of research results

The results of studies conducted in North Korea and Japan indicate that in these Asian countries, ARB-based combinations occupy leading positions among all consumed combined antihypertensive drugs [31, 32]. However, the authors of these works did not detail the structure of consumption of combined antihypertensive drugs, considering active ingredients and doses. According to the results of our study, it was found that in Ukraine, combinations of ACEI and diuretics, and ARB and diuretics occupy leading positions in the structure of consumption. The presented research results make it possible to detail the structure of consumption of combined drugs for hypertension, considering the number of active ingredients and their doses in Ukraine, as well as the dynamics of their consumption over the years.

By median share of consumption, the following fixed-dose combinations were captopril/HCTZ (50 mg/25 mg) – 29.04%; enalapril/HCTZ (10 mg/25 mg) 11.74%; lisinopril/HCTZ (10 mg/12.5 mg) 11.64% and perindopril tertbutylamine with indapamide (8 mg/2.5 mg) – 11.42% among ACEI and diuretic combinations; valsartan/HCTZ (160 mg/12.5 mg (40.02%); and 80 mg/12.5 mg (29.07%); losartan/HCTZ (50 mg/12.5 mg) 11.30% among ARB and diuretic combinations; lisinopril/amlodipine (5 mg/5 mg) 15.25% and 10 mg/5 mg – 11.98%; perindopril arginine and amlodipine (5 mg/5 mg) 13.77%; and perindopril tertbutylamine and amlodipine (4 mg/5 mg) 11.08% of all ACEI and CCBs combinations; and valsartan/amlodipine, in all three available doses (160 mg/5 mg, 80 mg/5 mg and 160 mg/10 mg) 43.71%; 31.36% and 20.32%, respectively, among ARB and CCB combinations had the highest median consumption share rates in each respective combination drug group. According to the current legislation of Ukraine, combined antihypertensive drugs can be included in reimbursement programs after successfully passing the Medical Technology Assessment and including this drug in the National List of main drugs [33]. However, the initiator of the HTA may be the Ministry of Health of Ukraine, the National Health Service of Ukraine, or the applicant, i.e. the manufacturer or representative of the manufacturer [34]. In our opinion, the presence of several manufacturers of the same combined antihypertensive drugs may be a kind of deterrent factor in the context of initiating HTA for these drugs. We suggest that the available results obtained during the implementation of this study can serve as a consolidating factor for domestic and foreign manufacturers of combined antihypertensive drugs, which will accelerate the initiation of HTA with the further aim of including these combined drugs in reimbursement programs. Considering the above, we propose to use the obtained results of the analysis of the structure of consumption of combined AH drugs for further planning and implementation of clinical and economic studies in the context of discussing the issue of expanding the list of combined AH drugs for the treatment of AH, which are subject to reimbursement in Ukraine. However, further development of effective management decisions on updating the list of combined AH drugs, which are reimbursed, at the national level, must have an appropriate scientific, methodological and economic justification, and must include a public discussion of this issue among clinical and scientific experts in the treatment of AH.

Practical significance. The results of this study may become a scientifically sound basis if the Ukrainian government bodies that form health policy consider the need to expand the nomenclature (list) of combined antihypertensive drugs in the form of fixed combinations in the National List of main drugs, in particular with the aim of their further inclusion in reimbursement programs, in compliance with all applicable legislative requirements, in addition to those combinations that are already included in the National List of main drugs due to their presence in the WHO Model List of main drugs.

Study limitations. The study used data on retail sales of medicines in Ukraine, excluding the temporarily occupied territories of Donetsk, Luhansk, Zaporizhia, Kherson regions and the Autonomous Republic of Crimea, for a relatively short period of time – 4 years, which includes the period of the full-scale invasion of the Russian Federation into the territory of Ukraine, which caused a significant humanitarian crisis in early 2022. These factors had their impact on the formation of a statistical base that could potentially be used in the analysis of the consumption structure across the country. In addition, data from only one information base was used, which may also have a limiting effect on the results obtained. The study also did not consider the consumption of those antihypertensive drugs that entered the territory of Ukraine as humanitarian aid during the full-scale invasion of the Russian Federation.

Prospects for further research. Given the implementation of the state program "Affordable Medicines", as well as the availability of mono-component drugs, two- and three-component combined drugs for the treatment of hypertension on the Ukrainian market, research into the structure of their consumption, and further analysis of dynamics and changes, with the aim of adjusting and additions to reimbursement programs, are promising.

6. Conclusions

The results of the analysis of retail sales showed that combined ACEI and diuretic drugs are the most consumed among all two-component combined drugs for the treatment of hypertension in Ukraine in 2020–2023. An in-depth analysis of consumption, taking into account the active substances and doses of combined antihypertensive drugs, allowed us to identify features in the formation of the indicated indicator – the median share of consumption of the combination of captopril + HCTZ in a dosage of 50/25 mg, which is usually used in medical practice as a quick-relief short-acting antihypertensive drug, was 29.04% – that is, almost a third of all drugs in this group.

By median share of consumption, the following fixed-dose combinations of enalapril/HCTZ (10 mg/25 mg) median 11.74%; lisinopril/HCTZ (10 mg/12.5 mg) median 11.64% and perindopril tertbutylamine with indapamide (8 mg/2.5 mg) – 11.42% among combinations of ACEI and diuretics; valsartan/HCTZ (160 mg/12.5 mg (median 40.02%); and 80 mg/12.5 mg (median 29.07%;); losartan/HCTZ (50 mg/12.5 mg) median 11.30% among ARB and diuretic combinations; lisinopril/amlodipine (5mg/5mg) median 15.25%; and (10mg/5mg) median 11.98% perindopril arginine and amlodipine (5 mg/5 mg) median 13.77%; and perindopril tertbutylamine and amlodipine (4 mg/5 mg) median 11.08%; from all ACEI and CCBs combinations; and valsartan/amlodipine, in all three available doses (160 mg/5 mg, 80 mg/5 mg and 160 mg/10 mg) median 43.71%; 31.36% and 20.32% respectively, among the combinations of ARBs and CCBs had the highest median consumption share in each respective group of combination drugs in Ukraine in 2020–2024.

We propose to recommend fixed doses of combined drugs of enalapril, lisinopril and valsartan with HCTZ, as well as combinations of lisinopril, perindopril arginine, perindopril tertbutylamine and valsartan with amlodipine for consideration and further clinical and economic studies on their use in the context of discussing the issue of expanding the list of drugs for the treatment of hypertension, which are subject to reimbursement in Ukraine, with combined drugs.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship or other, which could affect the study and its results presented in this article.

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Data availability

Data will be provided upon reasonable request

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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