ANALYSIS OF THE RANGE OF DRUGS FOR THE TREATMENT OF ARTERIAL HYPERTENSION PRESENTED ON THE PHARMACEUTICAL MARKET OF UKRAINE

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Introduction. In Ukraine, cardiovascular diseases (CVD) are the leading cause of death. According to this indicator, our country remains one of the world leaders. Moreover, the main risk factor among the population leading to premature death is high blood pressure (BP), which without proper treatment can lead to heart attack, stroke, kidney or heart failure, vision impairment, and other complications. Even a moderate increase in blood pressure is associated with a decrease in life expectancy [1]. People with high blood pressure need early detection and pharmaceutical care. Today, the drugs of choice in the treatment of hypertension (AH) are angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (BCCs), diuretics, β-blockers (BB) [2-4]. When choosing the tactics of CVD therapy, clinicians are primarily guided by modern international recommendations and national protocols, but they must also take into account the Ukrainian realities [2]. Given the above, the study of the market of medicinal products (MP) used in the treatment of hypertension is of particular practical importance. Such scientists as Yu. V. Baigush, D. V. Semenov, M. M. Slobodyanyuk [5, 6], Hroshovyi T.A. [7], Korinevska G.M. [8], Nemchenko A.S. [9], L.V. Yakovleva et al. [10] dealt with this problem. But this data needs to be updated. In the context of the pandemic caused by the coronavirus infection COVID-19 and the quarantine measures associated with it, the Ukrainian pharmaceutical market has undergone significant changes over the past two years. Thus, the question of studying the market of antihypertensive drugs was interesting in terms of the pandemic.

The aim of our work is to analyze the range of antihypertensive drugs presented on the pharmaceutical market of Ukraine in terms of the pandemic caused by coronavirus infection COVID-19, to justify the choice of the optimal drug.

Materials and methods. The analysis of the range of drugs presented on the domestic pharmaceutical market was performed following the State Register of Medicinal Products [11] and the Register of Medicinal Products Subject to Reimbursement [12]. The composition of drugs under international non-proprietary names (INN), which are presented in the "Affordable Medicines" program, was analyzed. Based on the results of the analysis, a group of antihypertensive drugs was identified, which was further studied. The analysis of the modern range of antihypertensive drugs presented on the domestic pharmaceutical market was conducted using the ATC classification system [13]. According to the ATC classification, the following groups were analyzed: C02 - hypotensives, C03 - diuretics, C07 - b-adrenoceptor blockers, C08 - calcium antagonists, C09 - agents that affect the renin-angiotensin system.

Methods of analytical-comparative, systematic, logical, graphic, mathematical, and statistical analysis were used.

Results and discussion. The pharmaceutical market is very dynamic. New drugs are constantly appearing on the market, which requires a comprehensive analytical study.

In order to increase the availability of pharmaceutical care, the Government launched the Affordable Care Act in April 2017, under which CVD patients can receive certain drugs free of charge or at a small additional cost. To date, the list of drugs used in the treatment of hypertension the cost of which is fully or partially reimbursed from the state budget includes 12 INNs, namely amlodipine, atenolol, bisoprolol, verapamil, hydrochlorothiazide, enalapril, carvedilol, metoprolol, nifedipine, spironolactone, furosemide. A total of 151 trade names of drugs, which are presented in the form of tablets and film-coated tablets.

According to the State Register of Medicinal Products of Ukraine as of January 1, 2022, the group of antihypertensive drugs includes 665 medicinal products.

The assortment of domestic market of hypotensive drugs belonging to group C02 is formed by 50 drugs, of which 3.92% of the total range of the group are drugs containing the sum of alkaloids from the roots of Rauwolfia, drugs based on methyldopa - 1.96%, imidazoline receptor antagonists: clonidine - 9.80%, moxonidine - 21.57%, rilmenidine - 1.96%, guanfacine - 1.96%, antiadrenergic drugs, ganglioblockers: benzohexonium - 1.96%, adrenoceptor blockers - 29.41%, uradipil - 13.73%, other antihypertensive drugs based on riociguat - 9.80%. Also on the domestic market, there are 2 combined drugs with trade names Normatens No. 20 (ICN Polfa Rzeszów JSC, Poland) and Homviotensin No. 100 (Mauermann - Arzneimittel KG, Germany), which account for 3.92% of the total range of the group (Fig. 1).

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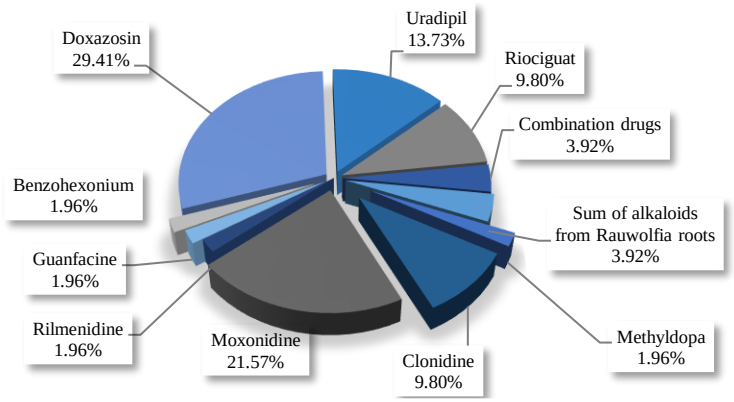

Fig. 1. The structure of the assortment of hypotensive drugs by active substances present on the pharmaceutical market of Ukraine.

The analysis has shown that 35.71% of the range of the study group are domestically produced drugs. A significant share is occupied by medicines of foreign production, which is 64.29% of the group's range. Foreign manufacture is represented by companies from such countries as Germany, (16.07%), France, Switzerland, Slovenia are 7.14 % each, the Republic of Belarus, Cyprus, USA, Austria - 5.36 % each, Hungary - 3.57 %, Poland - 1.79 % (Fig. 2).

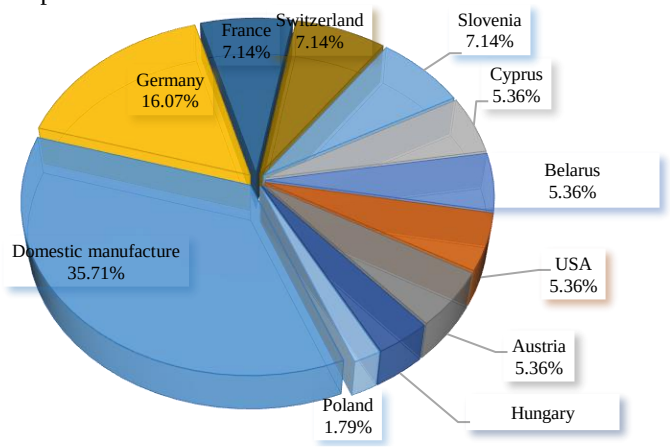

Fig. 2. Analysis of the structure of countries manufacturing hypotensive drugs, which are represented in the pharmaceutical market of Ukraine.

Diuretics have been widely used to treat patients with hypertension for about 50 years. According to prospective studies, treatment of hypertension with diuretics reduces the incidence of myocardial infarction by 14 - 16 %, stroke by 38 - 42 % [1].

There are 42 medicinal products on the domestic pharmaceutical market based on 7 active substances such as hydrochlorothiazide, indapamide, chlorthalidone, xipamide, torasemide, furosemide, spironolactone. The most widely represented drugs are drugs based on indapamide, accounting for 28.89% of the total range of the analyzed group. The share of drugs based on torasemide is 20.00% of the group, spironolactone - 15.56% of the group, hydrochlorothiazide - 13.33% of the group, furosemide - 11.11% of the group. The lowest number of proposals was recorded for drugs based on such active substances as xipamide - 6.67% and chlorthalidone - 4.44% of the range of the analyzed group (Fig. 3)

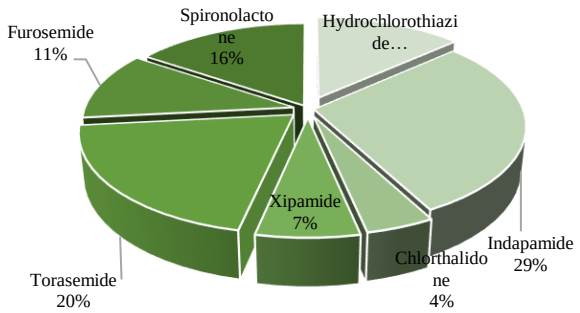

Fig. 3. The structure of the range of diuretic drugs by active substances on the pharmaceutical market of Ukraine.

The share of drugs manufactured by domestic manufacturers is 55.56%. Among foreign manufacturers, companies from Hungary predominate - 11.11%, Germany - 6.67%, Spain and Poland - 4.44% each. The share of other countries, including France, Luxembourg, India, the Czech Republic, Serbia, Slovenia, Bulgaria, Great Britain is 2.22% each (Fig. 4).

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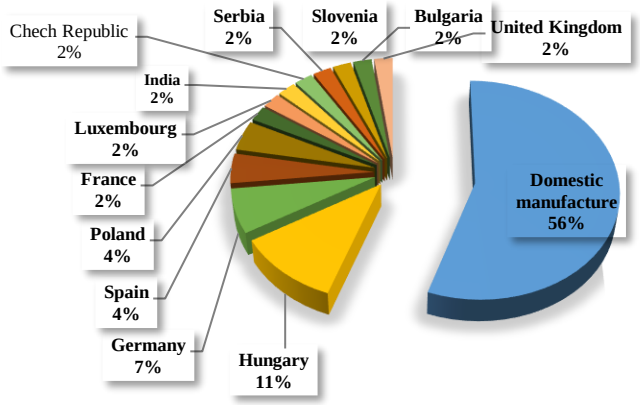

Fig. 4. Analysis of the structure of countries manufacturing diuretic drugs, which are represented in the pharmaceutical market of Ukraine.

b-adrenoceptor blockers have been used successfully in cardiology for over 40 years. b-blockers reduce the risk of cardiovascular complications and mortality, as well as sudden death [2]. In the pharmaceutical market of Ukraine, there are 93 mono-drugs of b-blockers based on 7 active substances such as propranolol, which is 4.30% of the range of the analyzed group, metoprolol - 15.05%, atenolol - 4.30%, betaxolol - 4.30%, bisoprolol - 33.33%, nebivolol - 7.53%, carvedilol - 31.18%. The largest number of proposals was recorded for drugs based on active substances such as bisoprolol and carvedilol (Fig. 5).

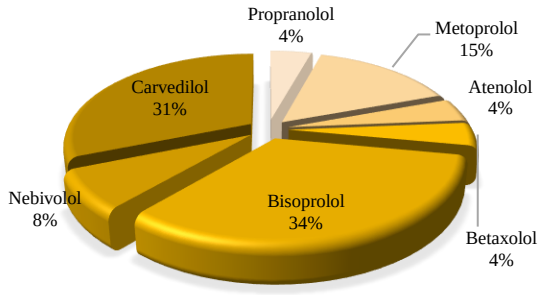

Fig. 5. The structure of the range of b-adrenoblockers by active substances on the pharmaceutical market of Ukraine.

Among the enterprises-manufacturers of b-adrenoblockers the share of Ukrainian companies is 38.54%, manufacturers from Germany - 11.46 %, India - 9.38 %, Hungary - 8.33%, Slovenia - 7.29 %, Romania - 5.21 %, Cyprus - 4.17 %, Macedonia, Luxembourg, and Sweden 3.13 % each, the Slovak Republic and Spain 2.08 % each, Malta and France 1.04 % each (Fig. 6).

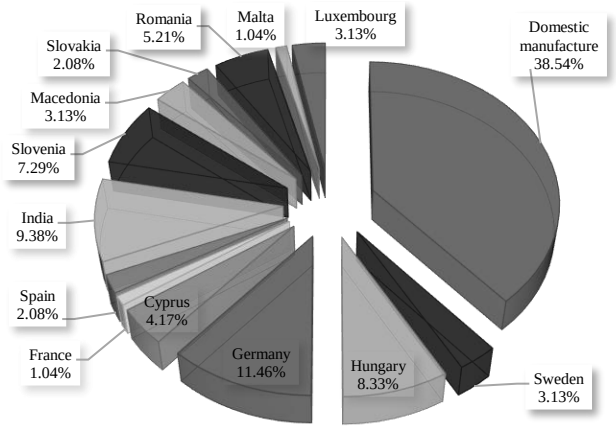

Fig. 6. Analysis of the structure of countries manufacturing b-blocker drugs, which are represented in the pharmaceutical market of Ukraine

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On the pharmaceutical market of Ukraine, there are 2 combinations of b-adrenoceptor blockers with thiazide diuretics with trade names Nebiar PLUS No. 30 (LLC "ARTERIUM LTD", Ukraine) and Nebilet PLUS No. 28 (Menarini International Operations, Luxembourg S.A.), 2 combinations of b-adrenoceptor blockers with other diuretics with trade names Dinorik-Darnitsa No. 10 (PJSC "Pharmaceutical company" Darnitsa ", Ukraine) and Tenorik No. 28 (Ipka Laboratories Limited, India), as well as 3-other combinations of Alotendine № 30 (CJSC Pharmaceutical Plant EGIS, Hungary), Tenochek № 20 (Ipka Laboratories Limited, India) and Tonorma No. 10, 30 (PJSC "Pharmaceutical Company" Darnytsa", Ukraine).

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Calcium channel blockers (CCBs), along with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, belong to new classes of antihypertensive drugs. Calcium channel blockers represent a heterogeneous group of drugs with different properties. Efficacy in lowering blood pressure in hypertension makes them first-line drugs [3, 4].

The structure of the range of calcium channel blockers, presented on the Ukrainian market, is formed by 72 drugs based on such active substances as amlodipine, which is 54.17% of the range of the study group, nifedipine - 18.06%, verapamil - 12.50 %, diltiazem, and lercanidipine 5.56% each, felodipine - 4.17% (Fig. 7). Also on the domestic market, there is one calcium channel blocker in combination with diuretics, under the trade name Arifam No. 30 (Le Laboratoiré Servier, France).

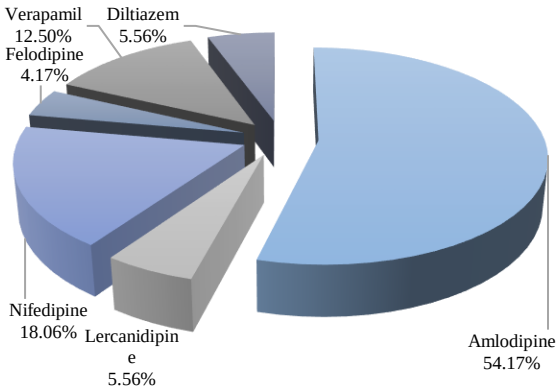

Fig. 7. The structure of the range of calcium channel blockers by active substances on the pharmaceutical market of Ukraine.

The share of drugs produced by Ukrainian manufacturers is 54.17%. Among foreign manufacturers, companies from India and Hungary predominate (9.72% each), Germany, Slovenia, and the Czech Republic have 6.94% each. The share of other countries, including Italy, Bosnia and Herzegovina, and Croatia, ranges from 3 to 1% (Fig. 8).

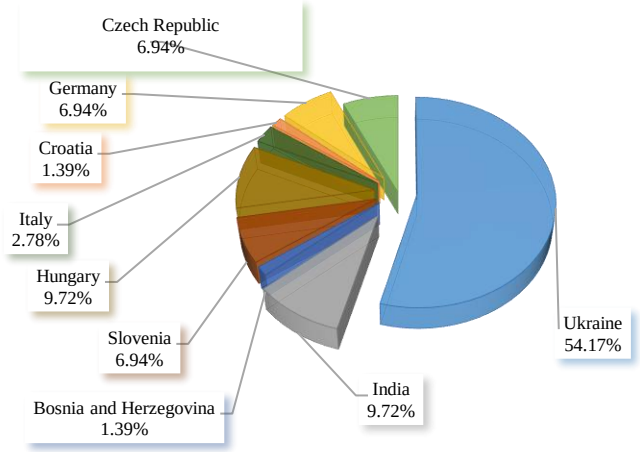

Fig. 8. Analysis of the structure of countries producing calcium channel blockers, which are represented in the pharmaceutical market of Ukraine.

Angiotensin-converting enzyme (ACE) inhibitors have become indispensable in the treatment of cardiovascular disease over the past 20 years. Angiotensin-converting enzyme inhibitors can block the activity of the renin-angiotensin system, as well as have an organoprotective effect and thus can be used to treat hypertension. The main property that makes angiotensin-converting enzyme inhibitors unique drugs is their ability to reduce mortality and prolong the life of patients with cardiovascular diseases [2].

According to the ATC classification, ACE inhibitors belong to the group C09 Agents acting on the renin-angiotensin system. Monopreparations of angiotensin-converting enzyme inhibitors C09A are 110 drugs based on 8 active substances: ramipril (26.36%), enalapril (23.64%), lisinopril (21.82%), perindopril (16.36%), captopril (5.45%), quinapril (3.64%), zofenopril (1.82%), enalaprilate (0.91%) (Fig. 9).

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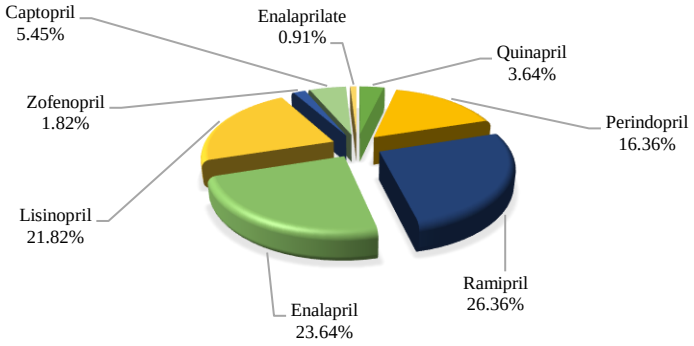

Fig. 9. The structure of the range of ACE inhibitor drugs by active substances on the pharmaceutical market of Ukraine.

Medicines produced by Ukrainian manufacturers are 39.09%. Most drugs are manufactured by foreign manufacturers - 60.91%. Dominating countries are Slovenia, with 16.36%, Poland - 8.18%, Cyprus and Hungary at 5.45% each, the United States and India at 3.64% each. Production from countries such as Germany, Jordan, Bosnia and Herzegovina, Luxembourg, France, Malta, the Republic of Macedonia, Italy, and Switzerland ranges from 3 to 1% (Fig. 10).

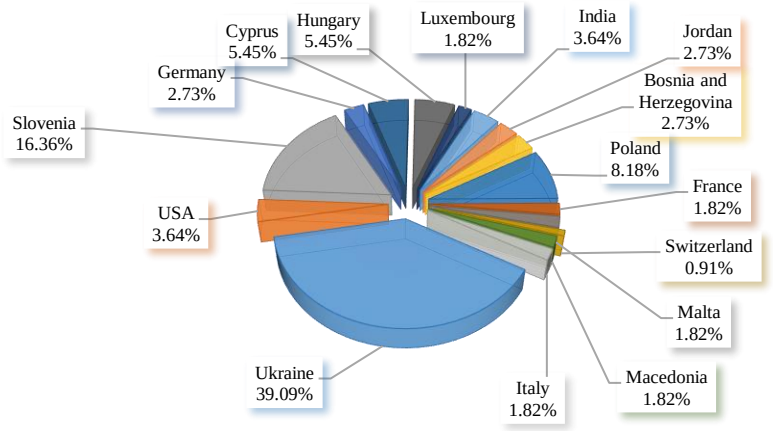

Fig. 10. Analysis of the structure of countries manufacturing ACE inhibitors, which are represented in the pharmaceutical market of Ukraine.

Combination drugs of ACE inhibitors form a subgroup C09B, which includes 115 drugs in combinations of ACE inhibitors with diuretics, combinations of ACE inhibitors with calcium channel blockers, and ACE inhibitors with diuretics and calcium channel blockers.

Combinations of lisinopril and diuretics are the most numerous in the domestic pharmaceutical market, accounting for 15.65% of the analyzed subgroup, perindopril, and CCB - 13.91% of the analyzed subgroup, ramipril, and diuretics - 13.04% of the analyzed subgroup, enalapril, and diuretics - 10.43 % of the analyzed subgroup, perindopril, and diuretic - 10.43%, perindopril, diuretic, and CCB - 10.43% of the analyzed subgroup. Pharmaceutical manufacturers also offer drugs containing a combination of ramipril with amlodipine (6.96% of the range of the subgroup), enalapril with lercanidipine (4.35%), lisinopril with amlodipine (4.35%), perindopril with bisoprolol (2.61%), trandolapril with verapamil (2.61%), captopril with hydrochlorothiazide (2.61%), quinapril with hydrochlorothiazide (1.74%), zofenapril with hydrochlorothiazide (0.87%) (Fig. 11).

A combination of enalapril with nitrendipine under the trade name Aeneas was presented by "Ferrer International, SA", Spain.

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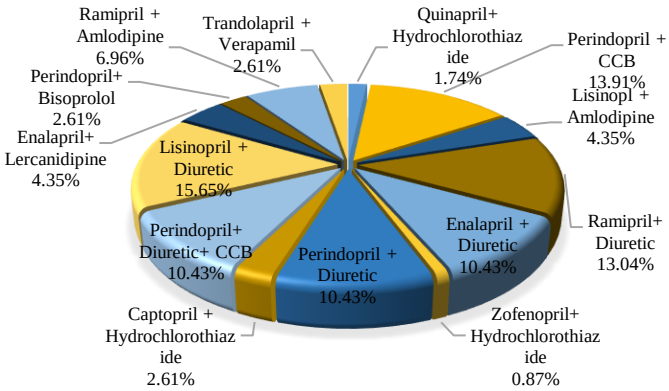

Fig. 11. Combinations of ACE inhibitors by active substances.

The share of drugs produced by Ukrainian manufacturers is 35.65%. Drugs produced by foreign countries account for 64.35%, which is distributed among the countries of Slovenia, (18.26% of the analyzed subgroup), France - 13.04%, Hungary - 10.43%, Germany - 5.22%. The percentage of drugs from other countries such as Cyprus, India, Ireland, Italy, Bosnia and Herzegovina, USA, Luxembourg, Switzerland, Malta, the Republic of Macedonia, Spain, the Republic of Serbia ranges from 3 to 1% of the analyzed subgroup (Fig. 12).

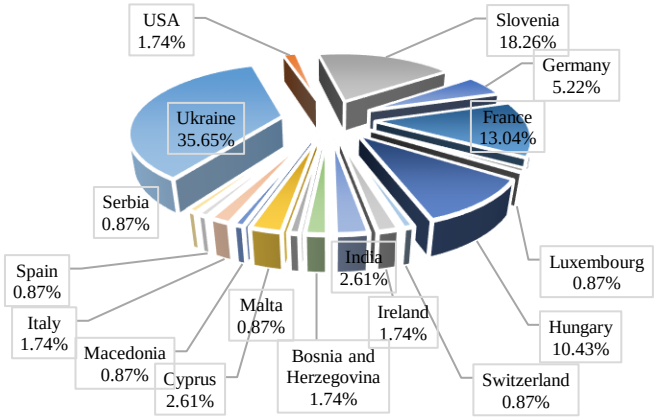

Fig. 12. Analysis of the structure of countries-manufacturers of combined ACE inhibitors, which are represented in the pharmaceutical market of Ukraine

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Angiotensin II antagonists are formed into subgroup C09C, which includes 73 drugs in the domestic pharmaceutical market. The study subgroup is formed of 8 active substances such as losartan, which is 30.14% of the range of the studied subgroup, valsartan - 27.40%, candesartan - 15.07%, telmisartan - 13.70%, irbesartan, olmesartan medoxomil, and azilsartan medoxomil 4.11% each. The lowest number of proposals was recorded for drugs based on eprosartan, which is 1.37% of the range of the studied subgroup. The structure of the range of the studied group by active substances is shown in Figure 13.

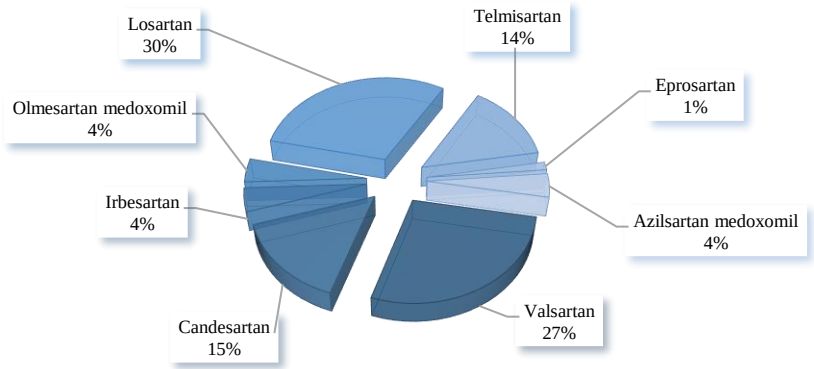

Fig. 13. The structure of the range of angiotensin II antagonists by active substances.

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The analysis showed that 24.66% of the range of the study group are domestically produced medicinal products. A significant share is occupied by medicines of foreign production, which is 75.34 % of the group's range. Foreign manufacture is represented by such countries as India (13.70%), Slovenia (12.33%), Hungary and Switzerland 10.96% each, the Republic of Northern Macedonia (6.85%), Cyprus (5.48%), Luxembourg (4.11%) each, Poland, Turkey and Bulgaria 2.74% each, France and Germany 1.37% each (Fig. 14).

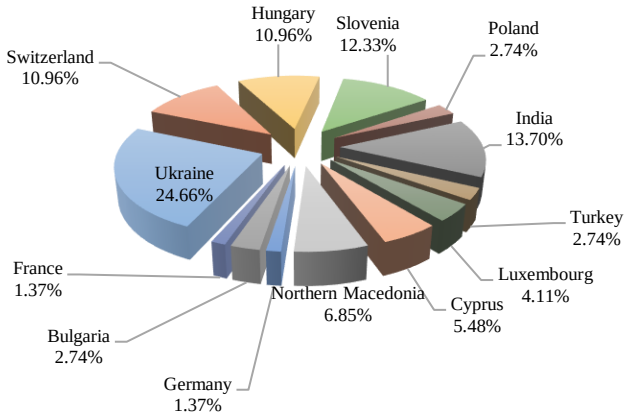

Fig. 14. Analysis of the structure of countries-manufacturers of angiotensin II antagonists, which are represented in the pharmaceutical market of Ukraine.

Combinations of angiotensin II antagonists with diuretics, as well as combinations of angiotensin II antagonists with calcium channel blockers according to the ATC classification belong to subgroup C09D. There are 95 combined drugs on the pharmaceutical market of Ukraine, namely combinations of valsartan with hydrochlorothiazide - 25.26%, valsartan with amlodipine - 16.84%, valsartan + diuretic + CCB - 13.68%, losartan with hydrochlorothiazide - 10.53%, telmisartan with hydrochlorothiazide - 7.37%, olmesartan medoxomil with amlodipine - 5.26%, irbesartan with hydrochlorothiazide - 4.21%, omlesartan medoxomil with hydrochlorothiazide - 4.21%, temisartan with amlodipine - 3.16%, valsartan with sacubitril- 3.16 %, candesartan with hydrochlorothiazide - 2.11 %, olmesartan medoxomil + diuretic + CCB - 2.11%, azilsatran medoxomil with chlorthalidone - 2.11% of the range of the analyzed subgroup (Fig. 15).

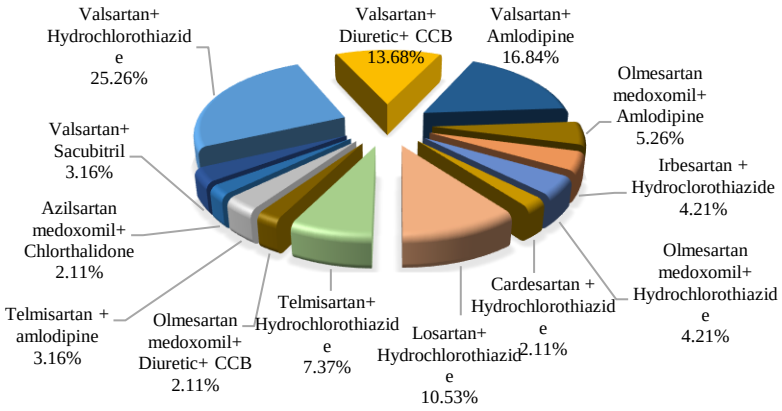

Fig. 15. Combinations of angiotensin II antagonists by active substances.

The share of drugs produced by Ukrainian manufacturers is 33.67%. Among foreign manufacturing companies, Slovenian companies predominate - 18.37%, followed by Switzerland - 17.35%, Germany - 7.14%. The share of other countries such as Hungary, Luxembourg, Cyprus, Malta, India, Poland, the Czech Republic, and Turkey ranges from 6 to 2% of the range of the analyzed subgroup (Fig. 16).

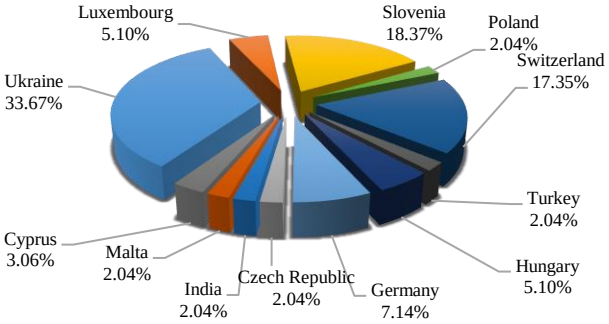

Fig. 16. Analysis of the structure of countries-manufacturers of angiotensin II antagonists combinations, which are represented in the pharmaceutical market of Ukraine.

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The next stage of the study was to analyze the range of drugs used to treat hypertension by dosage form.

It has been found that the studied drugs differ significantly in dosage forms. In the domestic pharmaceutical market, drugs are presented in seventeen dosage forms, among which the largest share is occupied by solid dosage forms, such as tablets - 55.77%, as well as film-coated tablets - 29.84%. Coated tablets - 4.05%, solutions for injection - 2.25 %; capsules - 1.50 %; hard capsules - 1.35%; prolonged-release film-coated tablets - 1.20 %; modified-release tablets and prolonged-release tablets - 0.90 % each; film-coated tablets with a retarded release - 0.45 %; prolonged-release hard capsules, oral drops, prolonged-release capsules, coated tablets with modified release and orally-dispersible tablets - 0.30 % each; film-coated tablets with modified release and concentrate for solution for infusion - 0.15 % each (Fig. 17).

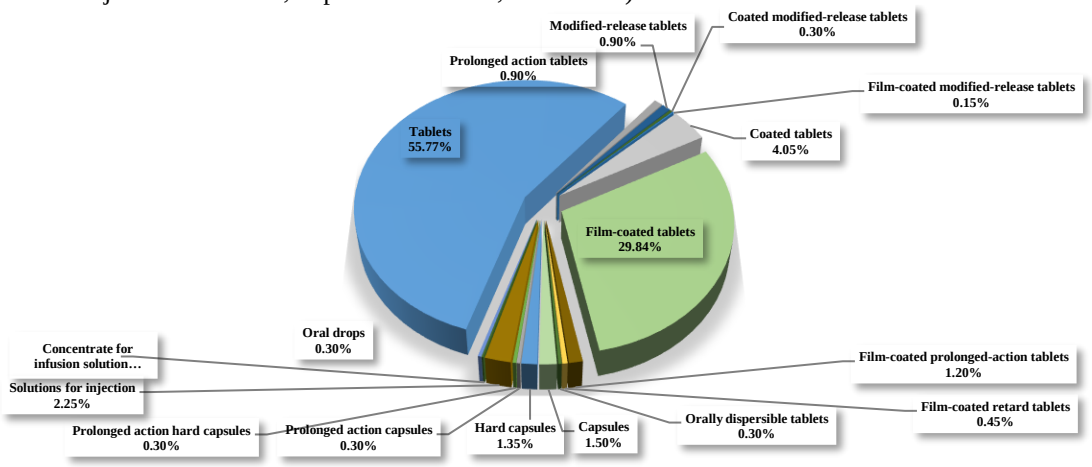

Fig. 17. Segmentation of the range of drugs used to treat hypertension depending on the dosage forms.

Based on the study of clinical treatment protocols and standards of medical care by primary care physicians for arterial hypertension, it was determined that enalapril is the "gold" standard for the ability to control blood pressure among ACE inhibitors [3, 4]. Therefore, in the future, we will plan to propose approaches to improve the technology of enalapril tablets.

Conclusions and prospects for further research.

1. As a result of the research, it has been established that the range of antihypertensive drugs presented in the State Register of Medicines of Ukraine is much wider than in the Register of Medicinal Products Subject to Reimbursement.
2. There is import dependence of the market segment of antihypertensive drugs. Most of the drugs of this group, represented on the pharmaceutical market of Ukraine are manufactured by European countries. But the share of drugs from domestic manufacturers that have joined the "Affordable Medicines" program is 63%.
3. Medicinal products of the studied groups are characterized by a significant diversity of dosage forms and are presented in seventeen forms, among which the largest part are solid dosage forms: tablets - 55.77%, as well as film-coated tablets - 29.84%; the percentage of other dosage forms ranges from 5 to 1%.
4. Enalapril was chosen as a promising drug for the Ukrainian market

Analysis of the range of drugs for the treatment of arterial hypertension presented on the pharmaceutical market of Ukraine

Verkhovod V., Kryklyva I., Karpenko L.

Introduction. High blood pressure (BP) is a major risk factor in the population leading to premature mortality. People with high blood pressure need early detection and pharmaceutical care. **The aim** of our work is to analyze the range of antihypertensive drugs presented on the pharmaceutical market of Ukraine in terms of the pandemic caused by coronavirus infection COVID-19, to justify the choice of the optimal drug. **Materials and methods.** The analysis of the assortment of antihypertensive drugs presented on the domestic pharmaceutical market was performed following the State Register of Medicinal Products (SRMP) and the Register of Medicinal Products Subject to Reimbursement (RMPSR), as of August 5, 2021. According to the ATC classification, the following groups were analyzed: C02 - hypotensives, C03 - diuretics, C07 - b-adrenoceptor blockers, C08 - calcium antagonists, C09 - agents that affect the renin-angiotensin system. Methods of analytical-comparative, systematic, logical, graphic, mathematical, and statistical analysis were used. **Results and discussion**. It has been found that according to the SRMP of Ukraine as of January 1, 2022, the group of antihypertensive drugs includes 665 trade names. The drugs are presented in seventeen dosage forms, among which the largest share is occupied by solid dosage forms, such as tablets (55.77%) and film-coated tablets (29.84%). 151 drugs in this group are included in the Affordable Medicines program and are presented in the form of tablets. For further research, enalapril was chosen as the "gold" standard among angiotensin-converting enzyme inhibitors. **Conclusions**. It has been established that the assortment of antihypertensive drugs presented in the SRMP of Ukraine is much wider than in the RMPSR. There is import dependence of the market segment of antihypertensive drugs. But the share of drugs from domestic manufacturers that have joined the "Affordable Medicines" program is 63%. The improvement of the technology of enalapril maleate tablets, which will be presented in the next publication has been substantiated.

Keywords: arterial hypertension, antihypertensive drugs, market analysis, enalapril

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