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ASPECTS OF THE USE OF ANTIDIABETIC DRUGS IN PHARMACEUTICAL PRACTICE ON THE BASIS OF RATIONAL PHARMACOTHERAPY

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Summary

The aim of the article. To study of the incidence of diabetes mellitus in Ukraine and to determine the prospects for the use and pharmaceutical development of antidiabetic drugs.
Materials and methods. Data from the State Registers of Medicinal Products of Ukraine, of Wholesale and Retail Prices for Medicinal Products declared in Ukraine under an international non-proprietary or generic name (01.01.2024). Were used: systematic and comparative analysis, processing and synthesis, and generalization to determine the forecasted prospects.
Results. In Ukraine the number of diabetes patients increased by 11 % in the group of children and adolescents; in the group of elderly patients – by 12.5 %, among the adult working – 20 %, diabetes of the II type predominates.
The trend of increase in the number of studies on the search for therapeutic alternatives for the treatment of type II diabetes and list of medicines on the pharmaceutical market has been revealed. In Ukraine drugs for oral use include APIs of the following pharmacological groups: sulfonylureas; meglitinides; biguanides; thiazolidinedione; α-glucosidase inhibitors; DPP-4 inhibitors; SGLT-2 inhibitors. Mechanism of action of the new class of oral hypoglycemic agents, approved by the FDA, consists in blocking SGLT-2 proteins from the proximal convoluted tubule in the kidney, leads to the prevention of reabsorption and excretion of the glucose molecule. This allows its use in combination with insulin and other antidiabetic drugs for the treatment of type I and II diabetes in patients of various age categories. According to the volume of clinical studies, SGLT-2 inhibitor SGLT-2 derivative gliflozin API drugs are the second largest group of antidiabetic drugs recommended for use by FDA and EMA regulatory bodies.
Conclusions. The pharmaceutical development of mono and combined drugs with APIs SGLT-2 inhibitors gliflozin derivatives in combination with APIs with metformin, DPP-4 inhibitors, APIs thiazolidinedione derivatives is promising for solving the problem of diabetes treatment and prevention of complications for patients of different age groups including working population in Ukraine.

Keywords: **diabetes, patients of different age groups, systematic and comparative analysis, antidiabetic drugs, active pharmaceutical ingredients, sulfonylurea derivatives; meglitinide derivatives; biguanide derivatives; thiazolidinedione derivatives; α-glucosidase inhibitors; DPP-4 inhibitors; SGLT-2 inhibitors; rational pharmacotherapy, therapeutic effectiveness; safety of use**

INTRODUCTION

The problem of the increase in the number of diabetes diseases is a medical and social problem that is becoming global in the modern world and requires an effective solution, first in medical supply based on rational pharmacotherapy and support for patient safety.

There is an observed trend of increasing R&D studies on the development of drugs for the treatment of type I diabetes, which is 23 %, and from 2020, the number has increased to 33 %; type II – 57 %, from 2020 it will increase to 77 %) and diabetes of the mixed type – 10 % of the total number of drugs of leading pharmaceutical companies on the global pharmaceutical market [1].

The revealed trend is due to the fact that the number of diabetes diseases in the modern world is increasing and the number of patients with type II diabetes dominates [2].

FDA approved indications for oral hypoglycemic agents focus primarily on the treatment of type II diabetes. It should be noted that there are no FDA approved indications for oral hypoglycemic drugs, such as metformin, for the prevention of type II diabetes [3].

Most hypoglycemic drugs are designed to treat type II diabetes. It should be noted that α-glucosidase and α-amylase inhibitors, aimed at inhibiting carbohydrate-metabolizing enzymes, have been among the most thoroughly studied hypoglycemic drugs.

Although a large list of natural and synthetic substances have been investigated for their ability to correct the dysregulation of specific enzymes involved in the pathogenesis of type II diabetes, only a few of them have been approved for clinical use [3].

Available evidence suggests that some of these approved drugs may cause side effects, exacerbating health complications in patients with diabetes.

Therefore, it is important to develop cost-effective strategies for the production of new hypoglycemic agents that minimize side effects while maximizing efficacy, taking into account the molecular aspects of the progression of type II diabetes.

THE AIM OF THE STUDY

To carry out a study of the state of solving the problem of the spread of diabetes in Ukraine and to determine the prospects for the use and pharmaceutical development of antidiabetic drugs.

MATERIALS AND METHODS

Research materials – data from the State Register of Medicinal Products of Ukraine; information content of the Central Health Service of the Ministry of Health of Ukraine; data of the State Register of wholesale and retail prices for medicinal products declared in Ukraine under an international non-proprietary or generic name as of January 1, 2024. Research methods: in the conducted studies, methods of systematic and comparative analysis, generalization, statistical processing and synthesis were used in determining projected perspectives, design, tabular and graphical means of presenting results. To implement the goal and tasks of the research, software and electronic resources of ATX (Anatomical-Therapeutical-Chemical), ATC (Anatomical Therapeutically Chemical Classification System), BCS (Biopharmaceutical Classification System), Compendium, State Register of Medicinal Products of Ukraine were used; statistical data and clinical trial content data: https://www.wipo.int; https://www.dec.gov.ua; https://www.clinicaltrials.gov; https://www. ncbi.nlm.nih.gov; https://eacpt.org; https://bpspubs.onlinelibrary.wiley.com, by keywords – names of antidiabetic pharmaceuticals.

RESULTS

According to the official published data of the Ministry of Health of Ukraine for the period 2021-2023, as of January 1, 2024, in the group of children and adolescents, the number of patients with diabetes reaches about 10 thousand patients, according to the results of the study, it increased by 11 %. The results of the study on the prevalence of diabetes in the group of children of childhood and youth in Ukraine are shown in the diagram in fig. 1.

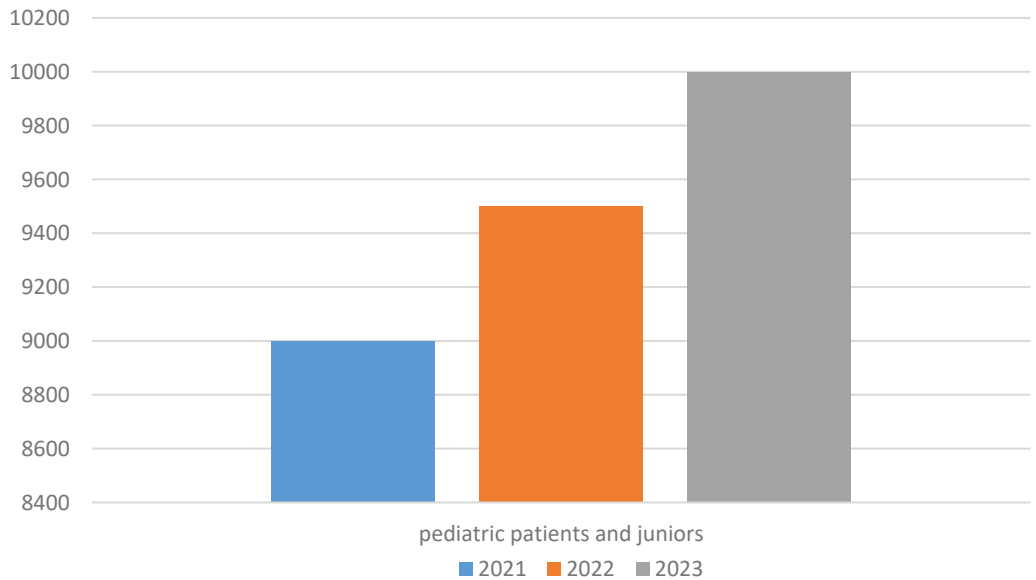

Fig. 1. Results of a study on the prevalence of diabetes in a group of children of childhood and youth in Ukraine

In the group of elderly patients, the number of diabetes patients is over 800,000, according to the results of the study, it increased by 12.5 %.

The highest prevalence of diabetes mellitus for the period 2021-2023 among the adult working population of 1.2 million people has increased by 20 %, diabetes of the second type dominates, and in conditions of war and exacerbation of the reaction to stress, the number of complications also increases [4; 5].

The results of the study on the prevalence of diabetes in groups of adult and elderly patients in Ukraine are shown in the diagram in fig. 2.

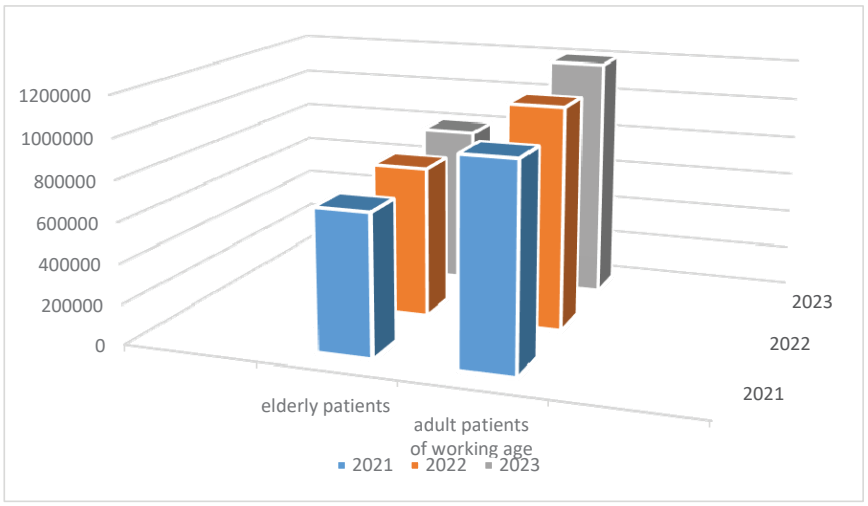

Fig. 2. The results of a study on the prevalence of diabetes mellitus in groups of adult and elderly patients in Ukraine

According to the results of the analysis, a trend of steady growth in the number of studies on the search for therapeutic alternatives for the treatment of type II diabetes and an increase in the list of pharmaceuticals on the world and Ukrainian pharmaceutical markets was noted.

On the pharmaceutical market of Ukraine as of January 1, 2024, oral preparations include active pharmaceutical ingredients of the following pharmacological groups: sulfonylurea derivatives; meglitinides; biguanides; thiazolidinedione; α-glucosidase inhibitors; DPP-4 inhibitors; SGLT-2 inhibitors [6; 7].

Diagram of the ratio of the positioning of drugs of certain pharmacological groups: sulfonylurea derivatives; meglitinides; biguanides; thiazolidinedione; α-glucosidase inhibitors; DPP-4 inhibitors; SGLT-2 inhibitors are shown in fig. 3.

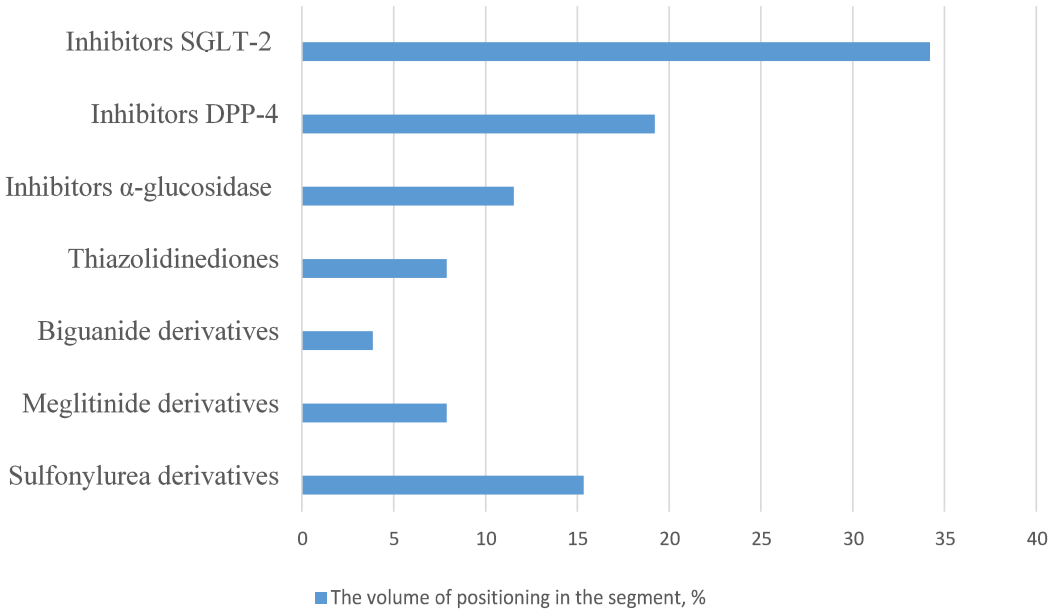

Fig. 3. The scope of positioning of oral antidiabetic drugs from API pharmacological groups on the pharmaceutical market for the period 2022-2024

According to the results of the research, the ratio of drugs presented by manufacturers in the groups of sulfonylurea derivatives, meglitinides, biguanides, α-glucosidase inhibitors is shown in the diagram in fig. 4.

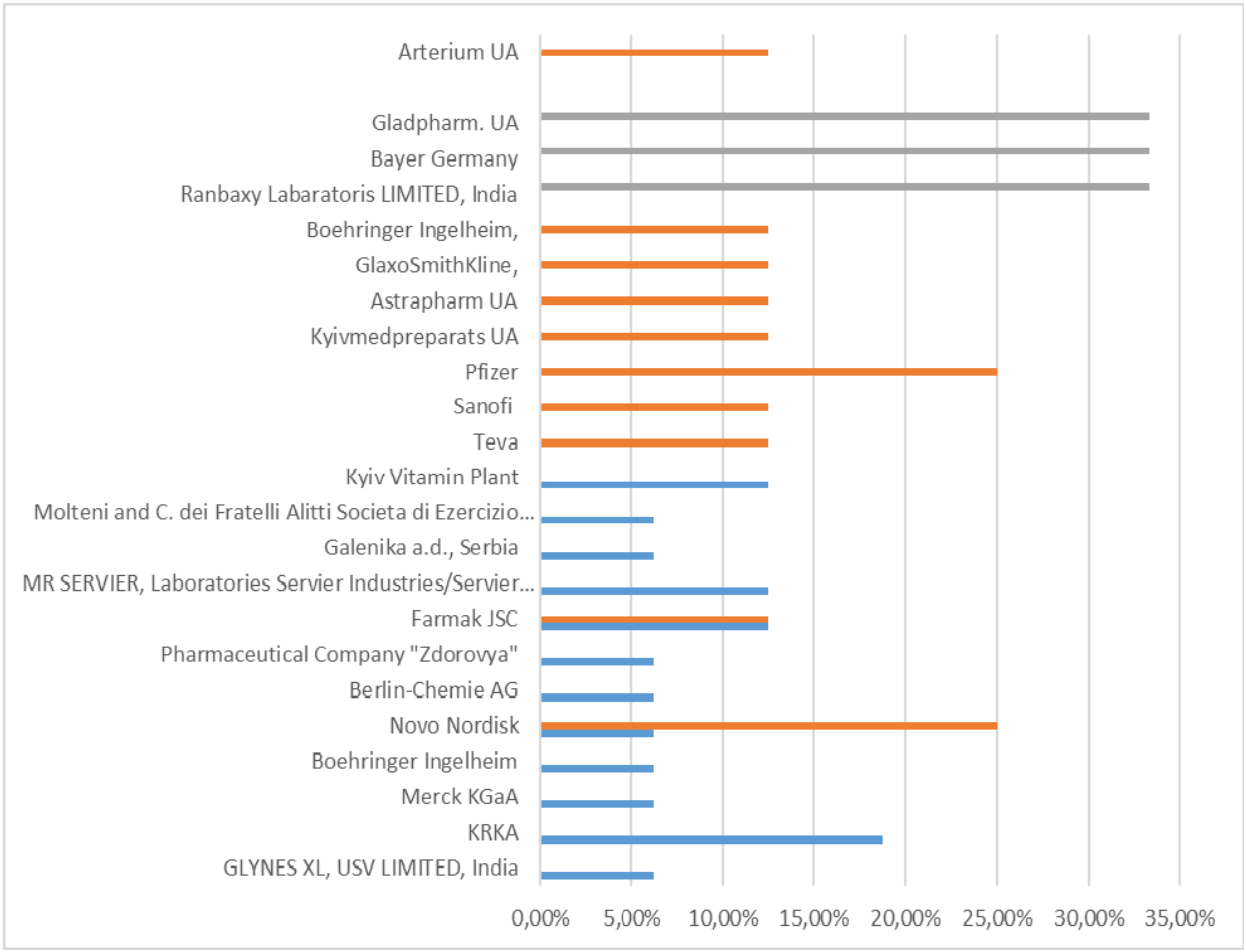

Fig. 4. The volume of supply of drugs with antidiabetic pharmacological drugs from API pharmacological groups of sulfonylurea, meglitinides, biguanides, thiazolidinediones derivatives, α-glucosidase inhibitors by manufacturers to the pharmaceutical market of Ukraine for the period 2022-2024.

The ratio of drugs presented by manufacturers in the group of DPP-4 inhibitors and SGLT-2 inhibitors is shown in the diagram in fig. 5.

It should be noted that in modern industrial pharmacy, the production of synthetic hypoglycemic drugs requires specialized technological conditions at a pharmaceutical enterprise and significant financial resources, since active pharmaceutical ingredients are labile compounds.

However, gliflozin represents a new class of oral hypoglycemic agents approved by the FDA for the treatment of diabetes with a unique mechanism of action – blocking SGLT-2 proteins from the proximal convoluted tubule in the kidney, which leads to the prevention of reabsorption and allows the glucose molecule to be excreted in the urine. Thanks to this mechanism of action, drugs whose active pharmaceutical ingredient is gliflozin derivatives reduce the level of blood glucose in the body and belong to the group of SGLT-2 inhibitors [8].

SGLT-2 inhibitors are the newest class of antidiabetic drugs, which are used in combination with insulin and other antidiabetic drugs in the treatment of diabetes mellitus I and II types in patients of various age categories, the most effective is the use in the group of adults to prevent complications and maintaining working capacity.

The API group of SGLT-2 inhibitors gliflozin derivatives is represented by the largest number of APIs on the world pharmaceutical market.

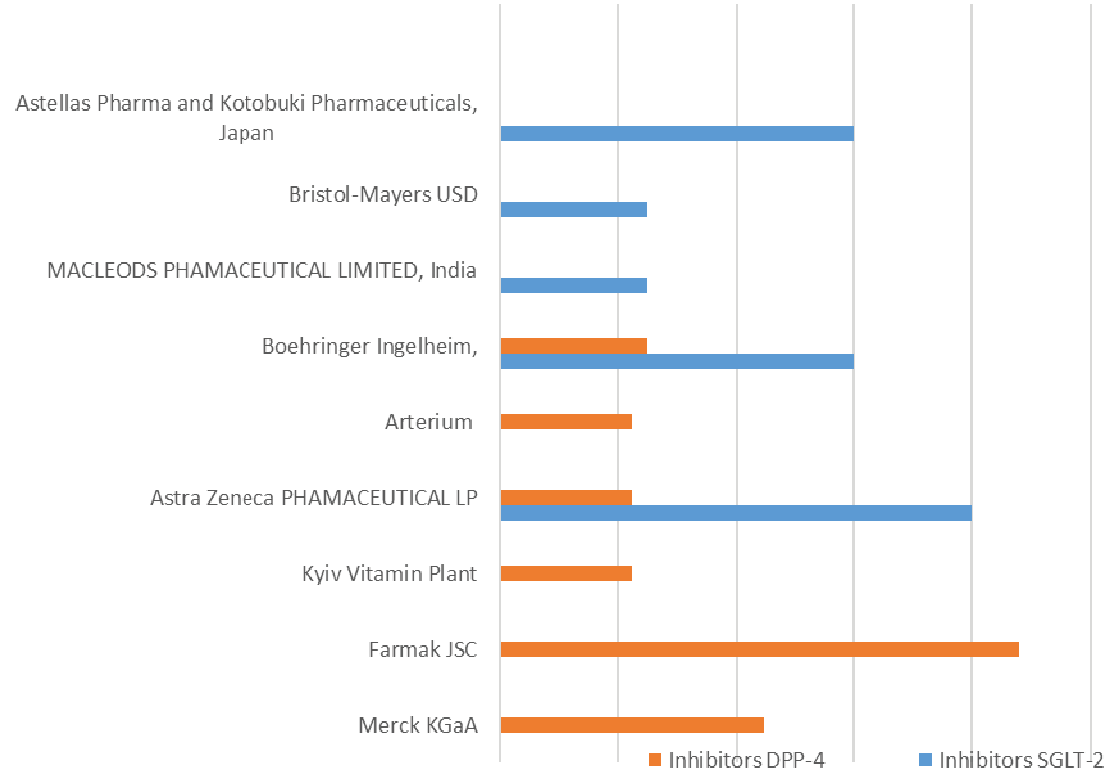

Fig. 5. The volume of supply of drugs from API pharmacological groups inhibitors DDP-4 and inhiditors SGLT-2 by manufacturers on the pharmaceutical market

Based on evidence-based medicine, drugs from the API of the pharmacological group of SGLT-2 inhibitors, derivatives of gliflozin, are used in combination with insulin and other antidiabetic drugs in the treatment of diabetes mellitus types 1 and 2, in combined regimens with metformin and DPP-4 inhibitors, as well as in combinations of all three and preparations of thiazolidinedione derivatives.

According to the volume of clinical studies, inhibitors SGLT-2, derivative gliflozin API drugs are the second largest group of antidiabetic drugs recommended for use by FDA and EMA regulatory bodies.

The list of pharmaceuticals from API class SGLT-2 gliflozin derivatives presented on regulated markets and approved by FDA and EMA includes: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, remogliflozin, luseogliflozin, tofogliflozin, sotagliflozin, as well as pharmaceutically acceptable salts; remogliflozin etabonate; sergliflozin etabonate [9; 10].

To determine the prospects for the development and research of the therapeutic effectiveness of new mono and combined drugs in the form of solid dosage forms for oral use, it was necessary to carry out a systematic analysis of the physico-chemical and pharmaco-technological properties of API class SGLT-2 pharmaceutically acceptable salts of gliflozin derivatives.

According to the results of the analysis, it was established that SGLT-2 APIs of pharmaceutically acceptable salts of gliflozin derivatives, since they have different solubility in water and differ in the degree of permeability, belong to II-III classes of the Biopharmaceutical Classification System (BSC), namely: canagliflozin, ipragliflozin belong to the II class of BSC; dapagliflozin, empagliflozin, ertugliflozin, remogliflozin, luseogliflozin, tofogliflozin, sotagliflozin, as well as their pharmaceutically acceptable salts belong to the III class of BSC.

Among SGLT-2 inhibitors, the specificity of the use of canagliflozin API drugs is that they are initially prescribed at a dose of 100 mg per day, which is gradually increased to 300 mg per day [9].

Whereas, the use of tablet forms with API – dapagliflozin is 5 mg or 10 mg per day the use of tablet forms with API – empagliflozin is 10 mg or 25 mg per day, depending on the state of the body, features of the pathogenesis and medical data of the patients.

DISCUSSION

Having analyzed the positioning on the pharmaceutical market and the use of pharmaceuticals from the API list of drugs of groups of biologically active substances that are used to create effective pharmaceuticals for the treatment of diabetes, it should be noted that gliflozin derivatives are new active pharmaceutical ingredients, their solid dosage forms for oral applications of urgent and prolonged action are just entering the pharmaceutical market.

However, according to the results of clinical studies, the therapeutic effectiveness of the use of mono and combined drugs with API derivatives of gliflozin for the category of adult patients, in which the number of diabetes diseases in the period 2021-2023, according to statistical data, is the largest.

Considering the fact that in the conditions of the war in Ukraine and the exacerbation of the patients' reaction to stress, type II diabetes mellitus dominates, the number of complications is also increasing, the need to develop and introduce new effective drugs to the pharmaceutical market is gaining importance.

Especially important is the confirmed effective use of mono and combined pharmaceutical preparations with API derivatives of gliflozin for the treatment and prevention of complications of diabetes in the group of adult patients – the working population.

According to the results of the analysis, the therapeutic effectiveness of the use of mono-pharmaceutical preparations with API pharmaceutically acceptable salts and ethers of dapagliflozin for all age groups of patients with type II diabetes, complex treatment and prevention of complications of diabetes I and mixed types was confirmed.

It is promising to develop and bring to the pharmaceutical market combined drugs with API derivatives of gliflozin – dapagliflozin and empagliflozin in combination with API of the pharmacological group of DPP-4 inhibitors, in particular sitagliptin and vildagliptin.

API class SGLT-2 preparations of gliflozin derivatives are the largest pharmacological group by the number of positioning names in the wholesale and retail segments of the global pharmaceutical market and the number of sales on regulated markets – the total number of APIs is 11, drugs – 35 in the form of solid dosage forms for oral use, while the number of registered pharmaceuticals in Ukraine is only 4 mono and 2 combined drugs with API dapagliflozin, empagliflozin and ipragliflozin.

The price level based on the results of the pharmacoeconomic analysis and price comparison of other antihyperglycemic drugs is not available for all categories of patients in Ukraine who need systemic use of such drugs, especially for the elderly. Therefore, it is necessary to optimize research on the development of new mono and combined drugs to improve their quality, therapeutic effectiveness, safety of use and availability of these drugs for the treatment of diabetes and prevention of complications in Ukrainian patients.

CONCLUSIONS

According to the results of research conducted in Ukraine, the number of diabetes patients increased by 11 % in the group of children and adolescents; in the group of elderly patients, the number of patients with diabetes increased by 12.5 %, the highest prevalence of diabetes among the adult working population of 1.2 million people increased by 20 %, diabetes of the second type predominates, and in conditions of war and exacerbation of the reaction to stress, the number of complications is increasing.

Among antidiabetic drugs, drugs from the API of the pharmacological group of SGLT-2 inhibitors derived from gliflozin are promising for use in the treatment of type I and II diabetes in patients of various age categories, the most effective is the use in the group of adults to prevent complications and maintain working capacity. The use of drugs with API derivatives of gliflozin is possible in combination with insulin and other antidiabetic drugs in the treatment of diabetes mellitus types 1 and 2, in combined schemes with metformin and DPP-4 inhibitors, as well as in combinations with drugs with API derivatives of thiazolidinedione, therapeutic effectiveness is proven.

According to the volume of clinical studies, SGLT-2 inhibitor SGLT-2 derivative gliflozin API drugs are the second largest group of antidiabetic drugs recommended for use by FDA and EMA regulatory bodies.

Therefore, the pharmaceutical development of mono and combined drugs with APIs SGLT-2 inhibitors gliflozin derivatives in combination with APIs with metformin, DPP-4 inhibitors, APIs thiazolidinedione derivatives is promising for solving the problem of diabetes treatment and prevention of complications for patients of different age groups and the working category of the population in Ukraine.

The prospects for further research. Prospects for further research are the rationale for the organization of the stages of pharmaceutical development of mono and combined drugs with API SGLT-2 inhibitors derivatives of gliflozin in combination with APIs with metformin, DPP-4 inhibitors, API derivatives of thiazolidinedione to solve the problem of diabetes treatment and prevention of complications for patients of different age groups and the working category of the population in Ukraine.

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The article is self-funded. The authors declare no conflict of interest.

COMPLIANCE WITH ETHICAL REQUIREMENTS

No human or animal subjects were involved in the preparation of this article, no informed consent was applied.

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Резюме

АСПЕКТИ ВИКОРИСТАННЯ АНТИДІАБЕТИЧНИХ ЗАСОБІВ У ФАРМАЦЕВТИЧНІЙ ПРАКТИЦІ НА ОСНОВІ РАЦІОНАЛЬНОЇ ФАРМАКОТЕРАПІЇ

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Мета: дослідження захворюваності на цукровий діабет в Україні та визначення перспектив застосування й фармацевтичної розробки препаратів протидіабетичної дії.
Матеріали та методи: дані Державних реєстрів лікарських засобів України; оптово-відпускних цін на лікарські засоби, що декларуються в Україні під міжнародною непатентованою або генеричною назвою (на 01.01.2024 р.). Використано методи системного та порівняльного аналізу, обробки, синтезу й узагальнення для визначення прогнозованих перспектив.
Результати: В Україні серед дітей та підлітків чисельність хворих на цукровий діабет зросла на 11 %, серед осіб похилого віку – 12,5 %, серед працездатного населення – 20 %, при цьому переважає цукровий діабет II типу.
Виявлено тенденцію до збільшення кількості досліджень з пошуку терапевтичних альтернатив для лікування цукрового діабету II типу та переліку лікарських засобів на фармацевтичному ринку. В Україні для перорального застосування використовують похідні сульфонілсечовини; меглітиніди; бігуаніди; тіазолідиндіон; інгібітори α-глюкозидази; інгібітори ДПП-4; інгібітори SGLT-2. Механізм дії нового класу пероральних гіпоглікемічних засобів, схваленого FDA, полягає в блокуванні білків SGLT-2 із проксимальних звивистих канальців у нирках, призводить до запобігання реабсорбції та виведенню молекули глюкози. Це дозволяє використовувати його в комплексі з інсуліном та іншими протидіабетичними препаратами для лікування цукрового діабету пацієнтів різних вікових категорій. За обсягом клінічних досліджень препарати з АФІ інгібіторами SGLT-2 – похідними гліфлозину є другою за чисельністю групою антидіабетичних препаратів, рекомендованих регуляторними органами FDA та EMA.
Висновки: Фармацевтична розробка моно та комбінованих препаратів з АФІ інгібіторами SGLT-2 похідними гліфлозину в поєднанні з метформіном, інгібіторами ДПП-4, похідними тіазолідиндіону є перспективною для вирішення проблеми лікування цукрового діабету та профілактики ускладнень у хворих різних вікових груп, зокрема, працездатного населення в Україні.

Ключові слова: **цукровий діабет, пацієнти різних вікових груп, системний і порівняльний аналіз, протидіабетичні засоби, діючі фармацевтичні речовини, похідні сульфонілсечовини; похідні меглітиніду; похідні бігуанідів; похідні тіазолідиндіону; інгібітори α-глюкозидази; інгібітори ДПП-4; інгібітори SGLT-2; раціональна фармакотерапія, терапевтична ефективність; безпека застосування**