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STUDY OF PHARMACEUTICAL PROVISION OF TYPE 2 DIABETES THERAPY IN UKRAINE

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INFORMATION

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ABSTRACT

The aim of the work. Analysis of legislation and guidelines of pharmaceutical providing of type 2 diabetes (T2D) patients in Ukraine and studying of the availability of the glucose-lowering drugs (GLD) for the treatment of this disease according to guidelines.

Materials and Methods. The objects of the study were domestic and foreign clinical guidelines on T2D therapy, the State Register of Medicines of Ukraine. Bibliosemantic, marketing, analytical, graphic, generalization analyses were used.

Results and Discussion. The current legislation of Ukraine allows doctors to use modern international clinical guidelines for the treatment of diabetes mellitus (DM), while the Unified Clinical Protocol for T2D approved by the Ministry of Health of Ukraine in 2012 remains in force. On the pharmaceutical market of Ukraine, 161 GLD are registered, which contain 16 INN names. Out of 27 existing INN combinations on the world market, 8 INN combinations are registered in Ukraine. The largest part (64.0 %) of the range of GLD registered in Ukraine is supplied by foreign manufacturers. Part of the registered assortment of GLD in pharmacies is absent.

Conclusion. A comparative analysis of the guidelines showed that the Unified Clinical Protocol T2D needed updating. The study showed that in Ukraine, a sufficient range of GLD was registered, which allows the use of modern schemes for the treatment of diabetes, according to the international guidelines.

Diabetes mellitus (DM) is a significant medical and social problem. According to the International Diabetes Federation (IDF), the number of diabetes patients in the world is 537 million adults (December 2021). In Ukraine, the prevalence of DM is 7.1 %. Most (87–95 %) are patients with type 2 diabetes (T2D) [1].

Metabolic disorders in diabetes cause the occurrence of cardiovascular diseases (CVD) [2]. With T2D, the risk of myocardial infarction, stroke, peripheral vascular disease, etc., is 2–4 times higher than in the general population [1].

Despite the wide selection of glucose-lowering drugs (GLD), pharmacotherapy of T2D remains an urgent problem. The complexity of treatment regimens and the side effects of existing GLD prompt the search for new drugs and optimal combinations of them. And the high cost of drugs in Ukraine causes an acute social problem, since the prevalence of T2D is especially high among the elderly, and early complications lead to rapid disability of able-bodied people.

Effective treatment can prevent the development of complications and premature death. Therefore, the

therapy of DM according to modern standards and the availability of GLD is crucial for improving treatment outcomes. According to modern trends in the treatment of diabetes, drugs that provide therapy should not only be effective, but also reduce the risk of developing complications and side effects.

Drug availability is a combination of two dimensions of availability: market availability and drug affordability. Ensuring the availability of drugs, the use of which is prescribed by the treatment standard, is their state registration in the country [3].

Despite the achievements of diabetology, compensation for the disease remains a difficult task, and as the duration of diabetes increases, the effectiveness of its therapy decreases. In Ukraine, 87 % of T2D patients are in a state of decompensation [4].

Therefore, it is actual to investigate pharmaceutical provision for the treatment of T2D.

The aim of the work is analysis of Legislation and guidelines of pharmaceutical providing of T2D patients in Ukraine and studying of the availability of the GLD for the treatment of this disease according to guidelines.

Materials and Methods. The objects of the study were recommendations and normative documents on T2D therapy (domestic and foreign clinical guidelines, recommendations of international organizations), the State Register of Medicines (http:// www.drlz.com.ua) and information on the presence of drugs (www.tabletki.ua, www.liki24.com) on January 10, 2022. Bibliosemantic, marketing, analytical, graphic, generalization analyses were used. Methodology for the implementation of the research purpose is present on the fig. 1.

Results and Discussion.

At the first stage of the study, domestic and foreign clinical guidelines and international recommendations for the therapy of T2D were analyzed and the assortment of GLD specified in these guidelines was determined. For the treatment of T2D in Ukraine, the Unified clinical protocol of primary and secondary (specialized) medical care for type 2 diabetes mellitus (2012) has been approved [5].

According to this Protocol [5] First line of therapy is metformin. For patients with CVD, drugs with a lower risk of hypoglycemia should be preferred, glibenclamide should be prescribed with caution because it increases the risk of hypoglycemia. Repaglinide are recommended for patients with unsystematic lifestyle. Alpha glucosidase inhibitors (acarbose) are prescribed for patients who cannot use other oral CLD. Do not prescribe thiazolidinediones (pioglitazone) to people with heart failure or those at high risk of fractures. Dipeptidyl peptidase 4 (DPP4) inhibitors (vildagliptin, sitagliptin, saxagliptin) are prescribed to patients with overweight/obesity, elderly people with a high risk of hypoglycemia. GLP1 receptor agonists (exenatide, liraglutide) are prescribed to obese patients.

To ensure the implementation of the protocol [5], the outpatient clinic of the general practice of family medicine must have drugs: biguanides (метformin), метformin/glibenclamide and metformin/glipizide combinations: sulfonylureas (glibenclamide, glipizide, gliquidon, gliclazide, glimepiride); repaglinide; alpha glycosidase inhibitors (acarbose).

Since 2017, the current legislation in Ukraine also allowed the use of international clinical guidelines of professional or national medical organizations of member states of the European Union, the United States of America, Canada and the Australian Union as New Clinical Protocols [6].

List of a clinical guidelines for the treatment of T2D which have been analyzed and drugs (by *International Nonproprietary Names* (INN) and ATC groups) have been indicated:

- American Diabetes Association (ADA). Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes Care* [7].
- Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Diabetes Canada Clinical

Fig. 1. Methodology for the implementation of the research purpose.

Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Diabetes Canada Clinical Practice Guidelines Expert Committee* [8].

- The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020 [9].
- National Institute for Health and Care Excellence (Great Britan) Type 2 diabetes in adults: choosing first-line medicines [10].
- Global Guideline for Type 2 diabetes, IDF [11].
- Managing older people with Type 2 Diabetes, IDF [12].
- Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care, IDF [13].
- Diagnosis and management of type 2 diabetes, WHO; 2020 [14].
- Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus, WHO; 2018 [15].

The study of the pharmaceutical component of clinical guidelines and recommendations for the treatment of T2D showed that most guidelines offered three lines of GLD therapy before switching to insulin therapy. Both in the domestic guideline and in some foreign and international recommendations [7, 9, 10, 12, 15], mainly only groups of GLD are indicated, but in some cases the INN of the drugs are also indicated [8, 11, 13, 14]. A comparative analysis of the international recommendations with the domestic Unified Clinical Protocol of T2D showed that mainly the specified groups of GLD met international standards, but the Ukrainian Clinical Protocol did not include sodium-glucose co-transporter 2 (SGLT2) inhibitors, which are specified in all modern recommendations.

Based on the analysis of domestic, foreign and international recommendations, a list of GLD was established (by INN and ATC groups). Thus, in the Ukrainian Clinical Protocol of T2D as well as in the international recommendations, metformin is proposed as the first line of therapy, which is the basis of T2D treatment, or sulfonylureas (in case of contraindications to metformin). Metformin has cardioprotective properties, and CVD is the leading cause of death from DM. Metformin also helps reduce body weight, which is important given the prevalence of obesity among the T2D population and the pronounced negative impact of excess weight on CVD risk [21]. But in modern international standards, in the first line of therapy given the contraindications to metformin, other groups of GLD are recommended: DPP4 inhibitors or pioglitazone, or sulfonylureas, or SGLT2 inhibitor [11]. Although the latest WHO reports claim that the use of DPP4 inhibitors, SGLT2 inhibitors, thiazolidinediones at the initial stage of therapy does not exceed the results of the initial use of metformin and sulfonylureas [14, 15].

It should be noted that the experts of the ADA in 2021 noted that the emphasis of treatment of patients with diabetes was shifting: doctors pay attention not only to glycemic goals, but also to the health of the heart and kidneys. If a patient has CVD, kidney disease or is at high risk of these complications, the ADA recommends the use of additional and/or alternative drugs: glucagon-like peptide-1 (GLP-1) analogues and SGLT2 inhibitors to reduce health complications, regardless of HbA1c level or metformin use. Compared to enhanced schemes of insulin therapy, the use of basal insulin in combination with GLP1 analogues has a powerful glucose-lowering effect and at the same time reduces the risk of hypoglycemia and counteracts weight gain. Therefore, today it is recommended not only to add basal insulin to GLP1 analogues, but also GLP1 analogues to basal insulin (if GLP1 analogues were not previously prescribed). ADA recommendations note a significant impact on disease control, the risk of its complications, and patient mortality from socioeconomic factors (unavailability of healthy food, homelessness, financial limitations, etc.), which must be considered when making clinical decisions [16].

Thus, on the basis of the conducted analysis and taking into account the achievement of new research results, the emergence of new GLD and their combinations, recommendations of modern treatment regimens and a focus on personalized therapy, the domestic Unified Clinical Protocol of T2D (2012) needs an urgent update.

Using the ATC/DDD Index 2022 guide [17] of the WHO Collaborating Center for Drug Statistics Methodology (Norwegian Institute of Public Health), the range of GLD was defined and structured for further analysis according to the ATC classification.

The group of drugs *A10B – Blood glucose lowering drugs, excl. insulins*, which according to the ATC classification is included in group *A – Alimentary tract and metabolism* (*A10 – Drugs used in diabetes*) as of February 10, 2022, was studied. Insulins, which are also used in the therapy of T2D, were not studied due to the presence of current publications by Ukrainian scientists [18, 19]. Medicinal plant, which are not specified in the 3 protocols, but are present on the market, were not included in the analysis [22, 23].

It was established that, considering the dosage, the number of GLD is 161 trade names (TN), which contain 16 names and 8 combinations of them according to the INN (Table 2). 64.0 % (103 TN) of the assortment of GLD on the Ukrainian market are foreign-made drugs. The leaders in the supply of GLD are: India (14 drugs), Poland (11 drugs), Germany (10 drugs), Italy (9 drugs), Turkey (8 drugs) and France (8 drugs) (Fig. 2).

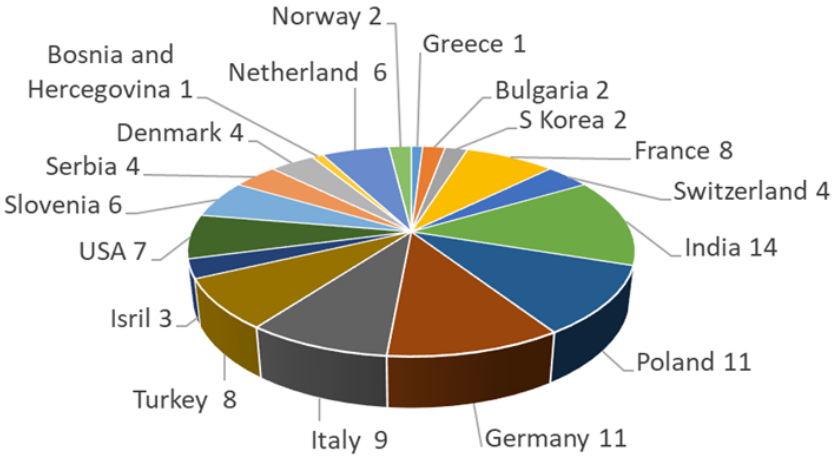

Fig. 2. Segmentation of GLD of foreign origin by country of manufacture in the pharmaceutical market of Ukraine (2022).

36.0 % of the assortment of GLD on the Ukrainian market are domestic-made drugs. In Ukraine, 8 pharmaceutical enterprises produce GLD. JSC "Farmak" (18 drugs) and GC “Kusum Pharm” (14 drugs) produce the largest number of GLD. Fig. 3 presents information on the number of GLD provided by pharmaceutical enterprises of Ukraine.

Table 1 «Assortment of drug group *A10B – Blood glucose lowering drugs, excluding insulins* on the pharmaceutical market of Ukraine (2022)» presents generalized information on the assortment of drugs of the *A10B* drug group on the pharmaceutical market of Ukraine according to the ATC classification.

Preparations containing 16 INNs are registered on the Ukrainian market, which is 29.6 % of the existing range of mono GLDs on the international market (according to ATC/DDD Index 2022 guide [17]). 27 INN combinations of GLD are on the world market, but only 8 INN combinations of them are registered in Ukraine, and combinations with three active substances are absent. Small groups in terms of the number of INNs are the subgroups of modern drugs: *A10B F – Alpha glucosidase inhibitors; A10B G – Thiazolidinediones; A10B J – Glucagon-like peptide-1 (GLP-1) analogues; A10B X – Other blood glucose lowering drugs, excl. insulins,* which are represented by only one name, which is 33.3 %, 25.0 %, 16.7 %, 14.3 % of the number of INNs existing on the pharmaceutical international market, respectively. There are no drugs of group *A10BC01 Sulfonylureas.*

As can be seen from the data in table 2 on the pharmaceutical market of Ukraine there are GLDs from all subgroups of group *A10B,* are registered. Almost a third of the entire range (32.2 %) consists of metformin preparations (group of *Biguanides*), represented by 52 TNs, both of Ukrainian and foreign production. This corresponds to the objectives of increasing social availability, that in addition to the availability of drugs, health care institutions should provide the opportunity to choose drugs and offer high-quality generics at a moderate cost [20].

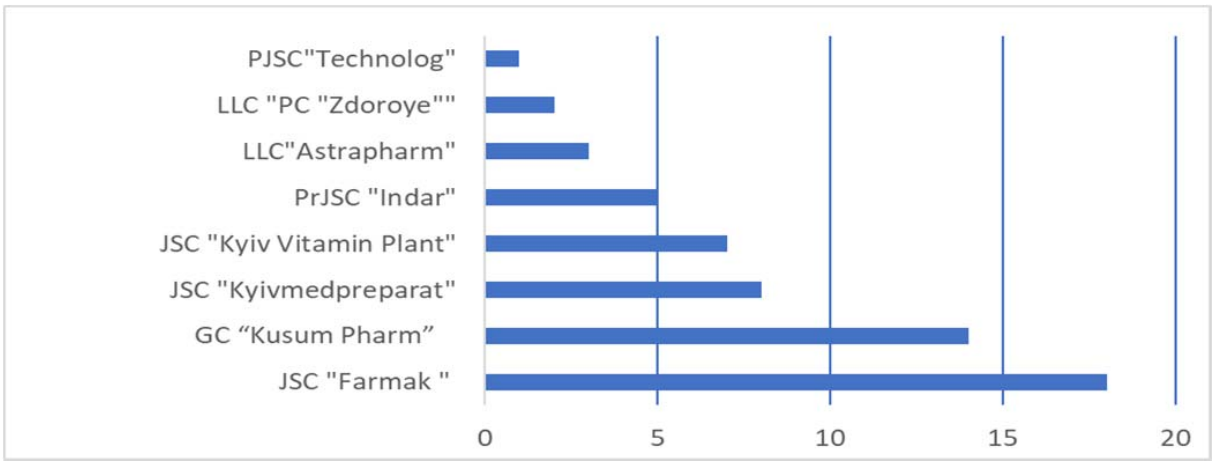

Fig. 3. The number of GLD depends on the Ukrainian manufacturer.

Table 1
Assortment of drug group *A10B – Blood glucose lowering drugs, excluding insulins* on the pharmaceutical market of Ukraine (2022)

Code ATC	International Nonproprietary Names of drugs	The number of registered GLD by trade name			
		unit		In total	
		Foreign	Ukrainian	unit	%
A10B A Biguanides					
A10BA02	Metformin	30	22	**52**	32.2
A10B B Sulfonylureas					
A10BB01	Glibenclamide	2	3	**5**	3.1
A10BB08	Gliquidone	1	–	**1**	0.6
A10BB09	Gliclazide	7	4	**11**	6.7
A10BB12	Glimepiride	24	15	**39**	24.1
A10B D Combinations of oral blood glucose lowering drugs					
A10BD02	Metformin/Glimepiride	1	2	**3**	1.9
	Metformin/Glibenclamide	5	1	**6**	3.8
	Metformin/Glipizide	1	–	**1**	0.6
	Metformin/Gliclazide	1	–	**1**	0.6
A10BD07	Sitagliptin/ Metformin	3	–	**3**	1.9
A10BD08	Vildagliptin/ Metformin	3	2	**5**	3.1
A10BD15	Dapagliflozin / Metformin	3	–	**3**	1.9
A10BD21	Saxagliptin / Dapagliflozin	1	–	**1**	0.6
A10B F Alpha glucosidase inhibitors					
A10BF03	Voglibose	–	2	**2**	1.3
A10B G Thiazolidinediones					
A10BG03	Pioglitazone	–	3	**3**	1.9
A10B H Dipeptidyl peptidase 4 (DPP-4) inhibitors					
A10BH01	Sitagliptin	3	2	**5**	3.1
A10BH02	Vildagliptin	2	2	**4**	2.4
A10BH03	Saxagliptin	2	–	**2**	1.3
A10BH05	Linagliptin	1	–	**1**	0.6
A10BH06	Gemigliptin	1	–	**1**	0.6
A10B J Glucagon-like peptide-1 (GLP-1) analogues					
A10BJ02	Liraglutide	2	–	**2**	1.3
A10B K Sodium-glucose co-transporter 2 (SGLT2) inhibitors					
A10BK01	Dapagliflozin	2	–	**2**	1.3
A10BK03	Empagliflozin	2	–	**2**	1.3
A10B X Other blood glucose lowering drugs, excl. insulins					
A10BX02	Repaglinide	6	–	**6**	3.8
In total		103	58	**161**	100 %

The *Sulfonylureas* drugs subgroup consists of 56 TN drugs, which according to the INN have only 4 names, including glimepiride, which is contained in 40 drugs (TN) of different manufacturers.

Full import dependence of the following GLD subgroups was established: *A10B J – Glucagon-like peptide-1 (GLP-1) analogues, A10B K – Sodium-glucose co-transporter 2 (SGLT2) inhibitors* and

A10B X – Other blood glucose lowering drugs, excl. insulins.

The analysis of the A10B group by dispersion medium showed that almost all GLDs are produced in the form of tablets (98.7 %). The liraglutide is produced as a solution for injections in cartridges inserted into a pre-filled multi-dose disposable syringe pen. It is important that in Ukraine there are tablets with a modified release, which are long-acting. For example, metformin has gastrointestinal side effects and a frequent dosing regimen that reduces adherence to treatment. To prevent this problem, XR metformin, which has a lower incidence of side effects and is administered only once daily, is recommended.

According to the results of the marketing research, it was established that of the INNs specified in the national guidelines, the pharmaceutical market of Ukraine today lacks: acarbose, exenatide, and the metformin/ pioglitazone combination. At the same time, despite the fact that the group of SGLT2 inhibitors is not specified in these guidelines, two drugs of this group (dapagliflozin, empagliflozin) are registered in Ukraine, which allows Ukrainian doctors to use modern schemes for the treatment of T2D. That is, a partial inconsistency of the assortment of GLDs that are in the Ukrainian doctor's arsenal with the list specified in the Unified Clinical Protocol T2D has been established.

In addition, when checking the actual presence of GLD on the market of Ukraine (information on the presence of drugs (www.tabletki.ua, www.liki24.com), it was established that part of the registered assortment of GLD is absent. Domestic drugs are present in a higher percentage (86%) than foreign ones (48%), which implies ensuring the stability of treatment with appropriate drugs.

The perspective of the study is to establish the socio-economic affordability of GLD.

Conclusion. 1. The current legislation of Ukraine allows doctors to use modern international clinical guidelines for the treatment of DM, while the Unified Clinical Protocol for T2D approved by the Ministry of Health of Ukraine in 2012 remains in force. A comparative analysis of the guidelines showed that the Unified Clinical Protocol T2D needed updating.

2. On the pharmaceutical market of Ukraine, 161 GLDs are registered, which contain 16 INN names, which is 29.6 % of the existing range of mono GLDs on the international market. Out of 27 existing INN combinations on the world market, 8 INN combinations are registered in Ukraine, there are no combinations of three active substances. Groups *A10BF; A10BG; A10BJ; A10BX* is represented by only one name.

3. The largest part (64.0 %) of the range of GLD registered in Ukraine is supplied by foreign manufacturers, the leaders of which are India, Poland, Germany, Italy, Turkey and France. In Ukraine, 8 pharmaceutical enterprises produce of GLD.

4. The study showed that in Ukraine, a sufficient range of GLD was registered, which allows the use of modern schemes for the treatment of diabetes, according to international guidelines.

5. Part of the registered assortment of GLD in pharmacies is actually absent. The actual presence of on the market of Ukraine was checked by information of online platform of pharmacies. Domestic drugs are present in a higher percentage (86 %) than foreign ones (48%), which implies ensuring the stability of treatment with appropriate drugs.

Конфлікт інтересів: відсутній.

Conflicts of interest: authors have no conflict of interest to declare.

ВИВЧЕННЯ ФАРМАЦЕВТИЧНОГО ЗАБЕЗПЕЧЕННЯ ТЕРАПІЇ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ В УКРАЇНІ

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Мета роботи. Аналіз законодавства та рекомендацій щодо фармацевтичного забезпечення хворих на цукровий діабет 2 типу в Україні та вивчення доступності (наявності) цукрознижувальних препаратів для лікування цього захворювання згідно з рекомендаціями.

Матеріали і методи. Об'єкти дослідження: рекомендації та нормативні документи щодо терапії цукрового діабету 2 типу, Державний реєстр лікарських засобів. Застосовували бібліосемантичний, маркетинговий, аналітичний, графічний, узагальнювальний аналізи.

Результати й обговорення. Чинне законодавство України дає змогу використовувати лікарям сучасні міжнародні клінічні настанови для лікування ЦД, одночасно продовжує діяти Уніфікований клінічний протокол лікування цукрового діабету 2 типу (2012 р.). На фармацевтичному ринку України зареєстровано 161 цукрознижувальний препарат, які містять 16 міжнародних непатентованих найменувань, що складає 29,6 % від існуючого асортименту міжнародного ринку моно-цукрознижувальних препаратів. Із 27 існуючих комбінацій міжнародних непатентованих найменувань на світовому ринку в Україні зареєстровано 8 їх комбінацій. Більшу частину (64,0 %) асортименту

зареєстрованих в Україні цукрознижувальних препаратів постачають іноземні виробники. Частина зареєстрованого асортименту цукрознижувальних препаратів в аптеках відсутня.

Висновок. Порівняльний аналіз настанов показав, що український Уніфікований клінічний протокол потребує оновлення. Дослідження показало, що в Україні зареєстровано достатньо цукрознижувальних препаратів, що дає змогу використовувати сучасні схеми лікування цукрового діабету згідно з міжнародними рекомендаціями.

Ключові слова: цукровий діабет; рекомендації з лікування цукрового діабету 2 типу; цукрознижувальні препарати; асортимент; доступність (наявність).

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