

Study of the influence of armed conflict on the reimbursement of oral glucose lowering drugs in Ukraine

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Abstract

The humanitarian crisis significantly affects the provision of medical and pharmaceutical care to PWD, and makes it difficult to predict its availability and affordability. It was established that despite the military actions in Ukraine, the reimbursement system is experiencing both negative and positive trends. Negative trends are: an increase in drug prices, the amount of patient co-payments, and a decrease in the number of glucose-lowering drugs that are subject to full reimbursement. Positive trends are: an increase in the amount of reimbursement and the number of glucose-lowering drugs that are included in the system reimbursements, including at the expense of extended dosage forms. The analysis showed that the war led to the introduction of positive changes – to increase the number of glucose-lowering drugs that are subject to full compensation.

Keywords

humanitarian disaster, armed conflict, diabetes mellitus, glucose lowering drugs, affordability, reimbursement

Introduction

In recent years, the intensity of armed conflicts in the world is increasing. Political instability and hostilities pose a global health problem (Garry and Checchi 2020). Military operations, the destruction of hospitals, pharmacies, and the priority of trauma treatment prevent proper access to the treatment of patients with chronic diseases (Crocker et al. 2021). Armed conflict poses serious challenges for patients, especially in developing countries where national disaster recovery plans are not developed, and health resources are insufficient (Leyh et al. 2018; Khan et al. 2019). The importance of noncommunicable disease treatment in humanitarian crises is noted in the 2018 Political declaration of the third high-level meeting of the General Assembly on the prevention and control

of non-communicable diseases and in the “Global action plan for the prevention and control of noncommunicable diseases 2013–2020”.

There are numerous publications about natural disasters and their consequences for the lives of patients living with diabetes (PWD) (Kishimoto and Noda 2013). However, there are limited data on diabetes mellitus (DM) during man-made disasters and military operations (Jaung et al. 2021). In this case it will be interesting to study changes of accessibility of medicines in countries where armed conflict is ongoing.

Today, the health care system of Ukraine functions under martial law. The prevalence of diabetes is 7.1%, most of which (87–95%) are patients with type 2 diabetes (T2D) (Diabetes Atlas 2021). The humanitarian crisis significantly affects the provision of medical and pharmaceutical

care to PWD, and makes it difficult to predict its availability and affordability (Slama et al. 2017). PWD experience difficulties in obtaining insulin and oral glucose lowering drugs (GLD), glucometers and test strips, therefore, patients cannot provide prompt treatment and self-monitoring of blood glucose levels. The burden of diabetes in emergency situations is often not taken into account, and the existing standards of medical care are not designed for such emergency situations, so the problems of patients with diabetes are not adequately addressed (Kehlenbrink et al. 2019; Vlasenko et al. 2022).

Drug availability and affordability are a component of the health care system and an important prerequisite for treatment results (Babar et al. 2019). Therefore, even in a situation of a humanitarian disaster, it is important to focus attention on ensuring patients' access to basic medicines (Beran et al. 2018).

The health care system can influence the affordability of drugs and medical services for the population through reimbursement. Reimbursement of the cost of pharmaceuticals increases their availability and affordability, but humanitarian disasters have an unforeseen impact on the implementation of measures in health care.

In order to improve the quality of life of patients with chronic diseases, such as DM, due to the increase in the physical availability and economic affordability of drugs, a reimbursement system, which included only insulin drugs, was introduced in Ukraine in 2016. The next stage of increasing the availability of drugs was the implementation of the "Affordable Medicines" program in 2017, which provided patients with T2D with oral GLDs (Zaliska et al. 2020).

Therefore, it is relevant to study how the reimbursement system in Ukraine has been function after February 24, 2022.

The aim

The purpose of the work is to investigate the changes in reimbursement of oral GLDs for the treatment of T2D since beginning humanitarian crisis in Ukraine.

Materials and methods

The objects of the study were the data of the State Register of Medicines (<http://www.drlz.com.ua>), Registers of marginal wholesale and retail prices for medicines that are subject to reimbursement under the program of state guarantees of medical care for the population for 2021–2022. ATX classification was used. The analysis of the range of preparations of Registers was carried out according to the offensive scheme: ingredients, medicinal form, manufacture. The amount of the defined daily dose (DDD) co-payment was calculated taking into account the data of the ATX/DDD index of the WHO Collaborating Center on Statistical Methodology. For comparative analyses math-

ematical calculations were used which based on data of retail prices per package, the amount of reimbursement for a DDD of pharmaceuticals, the amount of reimbursement for a package of pharmaceuticals, and the amount of co-payment per package.

Results and discussion

In Ukraine, a sufficient range of GLD was registered. According to research previously – glucose lowering drugs, with the exception of insulins (ATC code –A10B), 161 trade names (TN) of drugs are registered on the pharmaceutical market of Ukraine, which contain 16 names and 8 combinations of them according to the international non-proprietary name (INN). Modern medicines as Glucagon-like peptide-1 (GLP-1) analogues (Liraglutide) (1,3% of all TN GLDs) and Sodium-glucose co-transporter 2 (SGLT2) inhibitors (Dapagliflozin, Empagliflozin) (2,4% of all TN GLDs) are resisted as well. Study showed that a range of GLD allows the use of modern schemes for the treatment of diabetes, according to the international guidelines. But but only a small number 3 INN of GLDs are subject to reimbursement, which makes access to modern therapy for patients limited (Vlasenko et al. 2022).

The process of implementing the program involves the establishment by the Ministry of Health of Ukraine of the list of drugs that are reimbursed – the Drug Register. Registers are usually updated twice a year – at the beginning of the year and after six months. In 2021, the last Register was approved by the order of the Ministry of Health of Ukraine No. 1705 dated August 10, 2021 (Register 1). In 2022, the Ministry of Health of Ukraine determined the list of drugs that are reimbursed under the program of state guarantees of medical care for the population (Register 2, was not introduced) (order of the Ministry of Health of Ukraine No. 100, dated January 18, 2022), but in accordance with the permanent postponement of the implementation of this Register, it was active during 2022 the Register, which was approved by the order of the Ministry of Health of Ukraine dated August 10, 2021 No. 1705 (Register 1).

Thus, in connection with the introduction of martial law from February 24, 2022, the order that provided for changes at the beginning of 2022 was not implemented. The new active Register of drugs that are subject to reimbursement under the program of state guarantees of medical care for the population was approved by the order of the Ministry of Health of Ukraine No. 1931 dated October 27, 2022 (Register 3).

Table 1. The number trade names of GLD are subject to reimbursement.

N Register	The number trade names of GLD are subject to reimbursement			Total
	Metformin	Glibenclamide	Gliclazide	
Register 1	40	3	8	51
Register 2	43	3	8	54
Register 3	42	3	8	53

The Drugs registers include information: wholesale and retail prices per package, retail price per package, the amount of reimbursement for a DDD of pharmaceuticals, the amount of reimbursement for a package of pharmaceuticals, and the amount of co-payment per package. Based on the analysis of the data of the last three Registers, one of which has not been implemented, it is possible to investigate how the introduction of martial law affected the list of drugs subject to reimbursement, their price policy, the amount of reimbursement and the amount of co-payment from the patient.

The analysis of the three Registers showed that only 3 names of INNs are subject to reimbursement, which is 12.5% of all INNs registered in Ukraine for GLDs and their combinations. Metformin, glibenclamide and gliclazide are eligible for reimbursement. According to the latest Register, mainly drugs of the Ukrainian manufacturer are subject to reimbursement (Fig. 1). Local manufacturers ensure a stable supply of medicines, which is especially important in a humanitarian crisis.

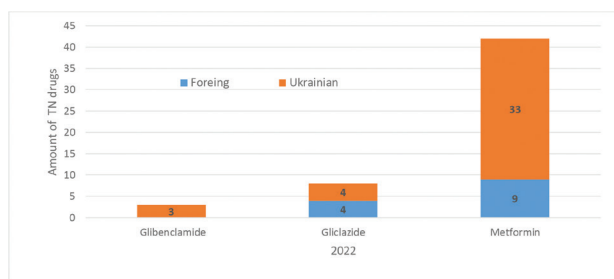


Figure 1. Segmentation of drugs subject to reimbursement in 2022 (Register 3) by manufacturer.

In previous years, a clear increase in the number of TN drugs for the treatment of diabetes, associated with a significant expansion of oral drugs, was established (Kostiuk et al. 2022). But analysis of the dynamics of GLDs that are subject to reimbursement for the period 2021–2022 shows that the number of TNs that are subject to reimbursement has almost not changed. The segmentation by manufacturer also did not undergo significant changes, but the percentage of Ukrainian production increased in 2022 by almost 5% compared to 2021. The list of manufacturers of GLD that are subject to reimbursement almost did not change. The reimbursement program includes: gliclazide preparations from two Ukrainian manufacturers and three foreign companies; glibenclamide preparations from three Ukrainian manufacturers and metformin preparations from 5 Ukrainian plants and 5 foreign pharmaceutical companies. The number of TN metformin drugs that are subject to reimbursement in 2022 increased and amounted to 80.8% of all metformin drugs registered in Ukraine (52 TN), and in 2021 it was 76.9%. (Vlasenko et al. 2022). A large number of TN increases the availability of medicines for patients.

According to the analysis of the 2021–2022 Registers, it was shown that the number of GLDs subject to reimbursement has almost not changed, but the number

of drugs subject to full reimbursement has decreased. Glibenclamide is subject to full reimbursement, which indicates its full economic affordability for patients. The number of gliclazide drugs that are subject to full reimbursement has increased from 1 to 4. According to Register 2, it can be said that it was planned to increase the number of TN of metformin, which would be fully reimbursed from 17 to 25 TN metformin, but the war prevented this. In Register 3, it is determined that only 15 GLDs are subject to full reimbursement, and the receipt of other drugs requires co-payment by the patient (Fig. 2). This shown negative influence of humanitarian crisis on number of full reimbursement drugs.

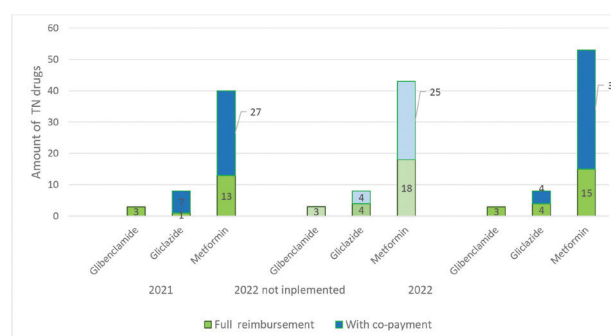


Figure 2. Segmentation of GLD in terms of full and partial reimbursement for 2021–2022.

An audit of the dosage of reimbursable GLDs showed that all dosage types that exist for these three study drugs are available. So, glibenclamide tablets are presented in 5 mg No. 30 and No. 50, and No. 100, which are provided by different manufacturers. Gliclazide is available in different dosages (30 mg, 60 mg and 80 mg) with different number of tablets in the package (No. 30, No. 60 and No. 90). The majority of gliclazide preparations (six TNs out of eight) with modified release (30 mg and 60 mg), both of domestic and foreign production. The largest number of reimbursable oral GLDs for T2D is metformin, which also has all dosage variations of 500 mg, 850 mg, and 1000 mg packaged with different numbers of tablets per pack (Fig. 3). The availability of various dosage of medicines provides an individual approach to the treatment of patients.

When analyzing the Registers, it can be seen that at the beginning of 2022, due to the war, the implementation of the reimbursement of extended-release forms of metformin, which were not available in 2021 (and previously years as well), was suspended. According to the latest Register 3, they are included in the list of drugs that are reimbursed. Their full reimbursement was planned, but the war did not make it possible to implement it, so today, when issuing prolonged medicinal forms, a co-payment from the patient is assumed.

Thus, meeting the needs of patients with T2D in various dosages, packaging and modifications with the three GLDs defined can be considered satisfactory. Despite the martial law, positive changes are being implemented regarding the access to prolonged forms of drugs that have

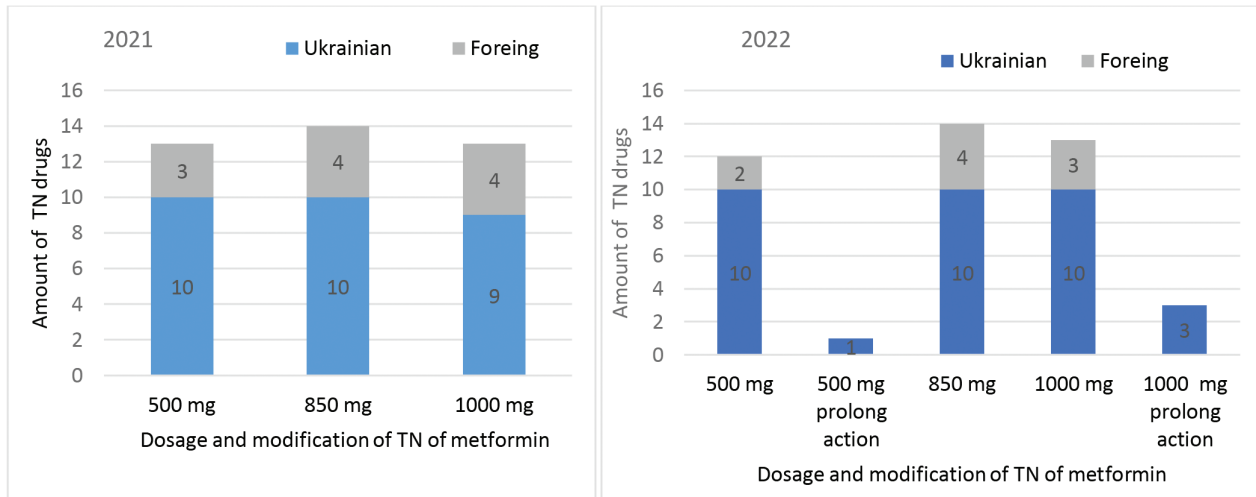


Figure 3. Distribution of the number of metformin drugs subject to reimbursement by dosage and manufacturer (2021, 2022).

better compliance when used by the patient. As known that extended-release forms increase patients' compliance (Romley et al. 2020). It's important to have opportunity to use these forms, especially in humanitarian crises when stable life is destroyed and people feeling a negative impact on mental health.

When comparing the retail prices specified in the Registers, it showed the dynamics of the retail price per package of GLD, which are subject to reimbursement for the period 2021–2022. It was established that the retail prices declared by the manufacturers increased in 2022 compared to 2021. At the beginning of 2022, the prices of most items (30 drugs) were not planned to increase (Register 2), but in 2022 the prices of GLDs increased compared to 2021. In 2022, prices did not change compared to the previous year only for 1.2% of drugs. The average index of price increase is 15.3%, while prices increased up to 10% for 18 drugs, from 10% to 20% – 14 drugs, and by more than 20% – 11 drugs. Army conflict made big negative impact to increases price because logistic supply chains were broken, part of storages and production manufacturers are destroyed, all this leads to a shortage of medicines increase in the cost of delivering medicines and as consequences price of medicines are increased.

When studying the data of the Registers, it was established that despite the war, the amount of reimbursement of the daily dose of drugs was increased (Fig. 4). Moreover, price of metformin increased by 4.8%, price of glibenclamide increased by 8.8%, and price of gliclazide increased more than twice as much. The increase in the reimbursement of gliclazide was planned for the beginning of 2022, but was postponed due to the war to the end of 2022. That is, regardless of the state of war, the government found an opportunity to increase the amount TN of reimbursement of oral GLD.

The implementation of the reimbursement program is influenced by the priorities of patients when choosing a drug in relation to the manufacturer and the amount of co-payment for the drug. Therefore, an audit of the

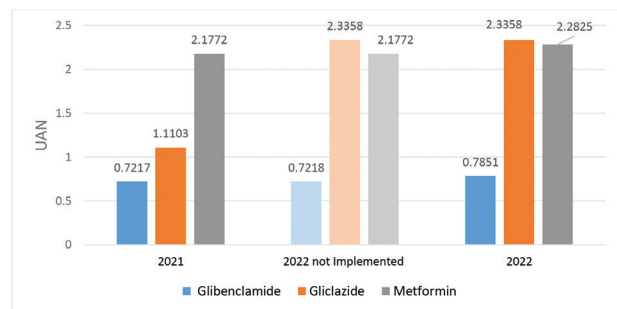


Figure 4. The amount of reimbursement of the DDD of GLD, which are subject to reimbursement (2021–2022).

price aspects of the GLD was additionally conducted, which included an additional payment for packaging. For unification, the amount of DDD co-payment was calculated for each drug that involves patient co-payment. The data of ATC/DDD index, dosage and packaging of GLDP were taken into account. The amount of surcharges for DDD of the drugs gliclazide and metformin, taking into account the dosage, the number of tablets in the package, is shown in Fig. 5 and Fig. 6 respectively.

In 2022, the number of fully reimbursed gliclazide drugs increased from 1 to 4, and co-payment of the DDD for gliclazide ranged from UAH 0.111 to UAH 2.510 in 2021, and from UAH 0.242 to UAH 1.614 in 2022. That is, the amount of co-payment for gliclazide has been reduced, which is especially important during a humanitarian crisis, when the financial burden on the patient has increased (Fig. 5).

8 metformin drugs out of 40, mainly of domestic production, included in the reimbursement program, are subject to full reimbursement. For comparison, Fig. 6 shows the amount of co-payments for DDD metformin drugs subject to partial reimbursement, which in 2021 will range from UAH 0.105 to UAH 1.576, and in 2022 – from UAH 0.213 to UAH 1.616. A more detailed analysis shows that the amount of co-payment for almost all metformin drugs has increased. Co-payment for foreign GLDs is more than for domestic ones.

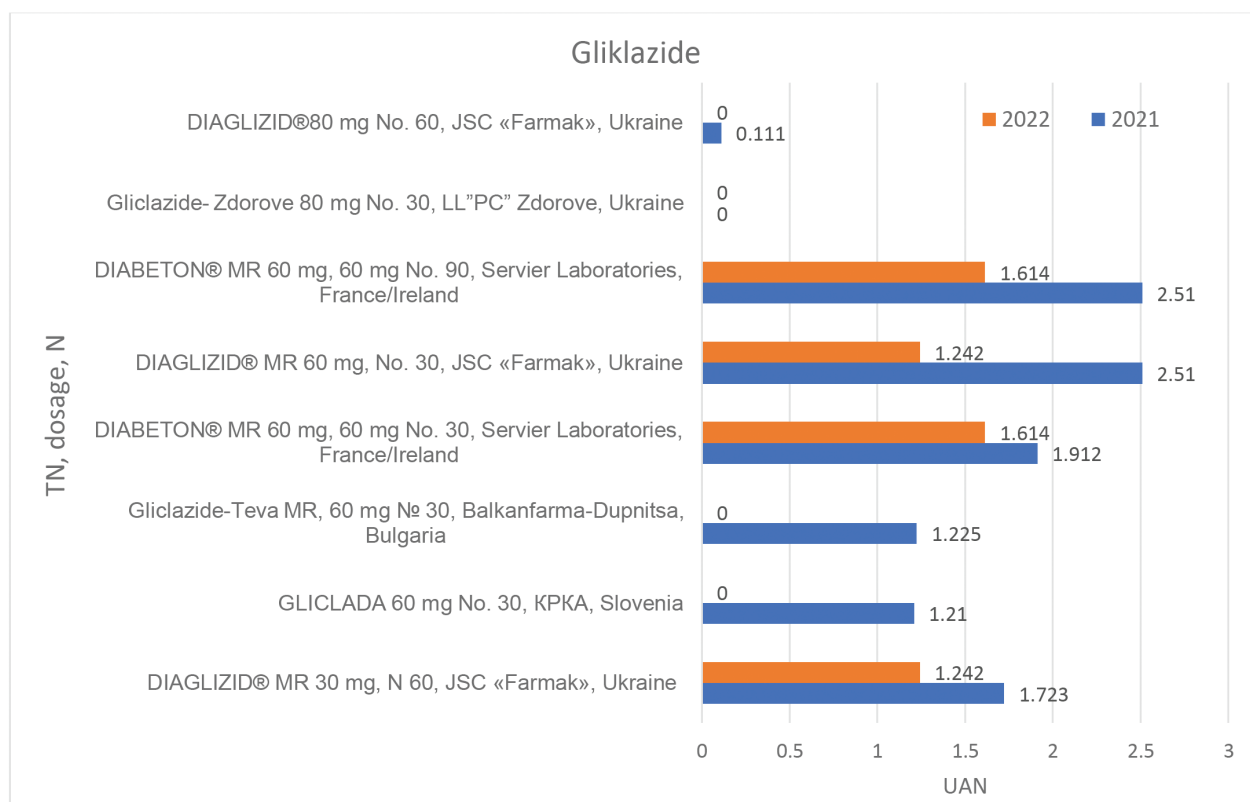


Figure 5. Dynamics of the amount of co-payment for DDD of gliclazide drugs (UAH) for 2021–2022.

Price of medicines influences on accessibility medicines especially in humanitarian crises. Increase part of compartment by patient could lead to changes medicines for treatment and in humanitarian crises when people have big negative impact to management of diabetes can lead for worse outcome of treatment.

Thus, the study showed that, despite the war, the availability of generic forms of metformin (the gold standard for the treatment of T2D (Luo et al. 2019), glibenclamide, and gliclazide is sufficiently high. The affordability of a wide list of generic GLDs meets the objectives of increasing the social availability of drugs, which consists not only in the availability of drugs, but also in ensuring the possibility of choosing a drug, its high-quality generics at a moderate cost (WHO Europe 2021).

It has been established that in Ukraine the number of registered oral GLDs for the treatment of T2D, including those according to modern recommendations, is quite significant (Vlasenko et al. 2022), but the list of CLDs whose cost is fully or partially reimbursed by the state is insignificant and includes only 3 INNs: metformin, gliclazide and glibenclamide .

It was established that from beginning of the armed conflict did not significantly change the number of reimbursed GLDs. The total number of drugs that are subject to reimbursement almost did not change, but the percentage of drugs of Ukrainian production increased by almost 5% in 2022 compared to 2021. The number of metformin drugs that are subject to reimbursement in

2022 increased and amounted to 80.8% of all registered in metformin drug use in Ukraine (52 TN), and in 2021 – 76.9% (Vlasenko et al. 2022).

The number of gliclazide drugs subject to full reimbursement increased from 1 to 4, but their number for metformin decreased. The war affected plans to increase the number of metformin drugs that would be fully reimbursed. In Register 3, only 15 drugs are subject to full reimbursement, and the receipt of other drugs requires a co-payment from the patient.

Metformin, gliclazide and glibenclamide tablets are represented by a sufficient range of drugs, respectively, in different dosages, modifications and packaging. Despite the war, extended-release forms of meformin are included in the reimbursement program. Before the war, their full reimbursement was planned, but today, when these drugs are dispensed, a co-payment from the patient is assumed.

The amount of copayment from the patient for gliclazide has been reduced, but increased for almost all metformin drugs. Co-payment for foreign CLDs is more than domestic.

Despite the war, the amount of reimbursement for the daily dose of CLDs was increased. The increase in reimbursement for gliclazide was planned for the beginning of 2022, but was postponed due to the war to the end of 2022. That is, regardless of the state of war, the government found an opportunity to increase the amount of reimbursement of oral CLDs.

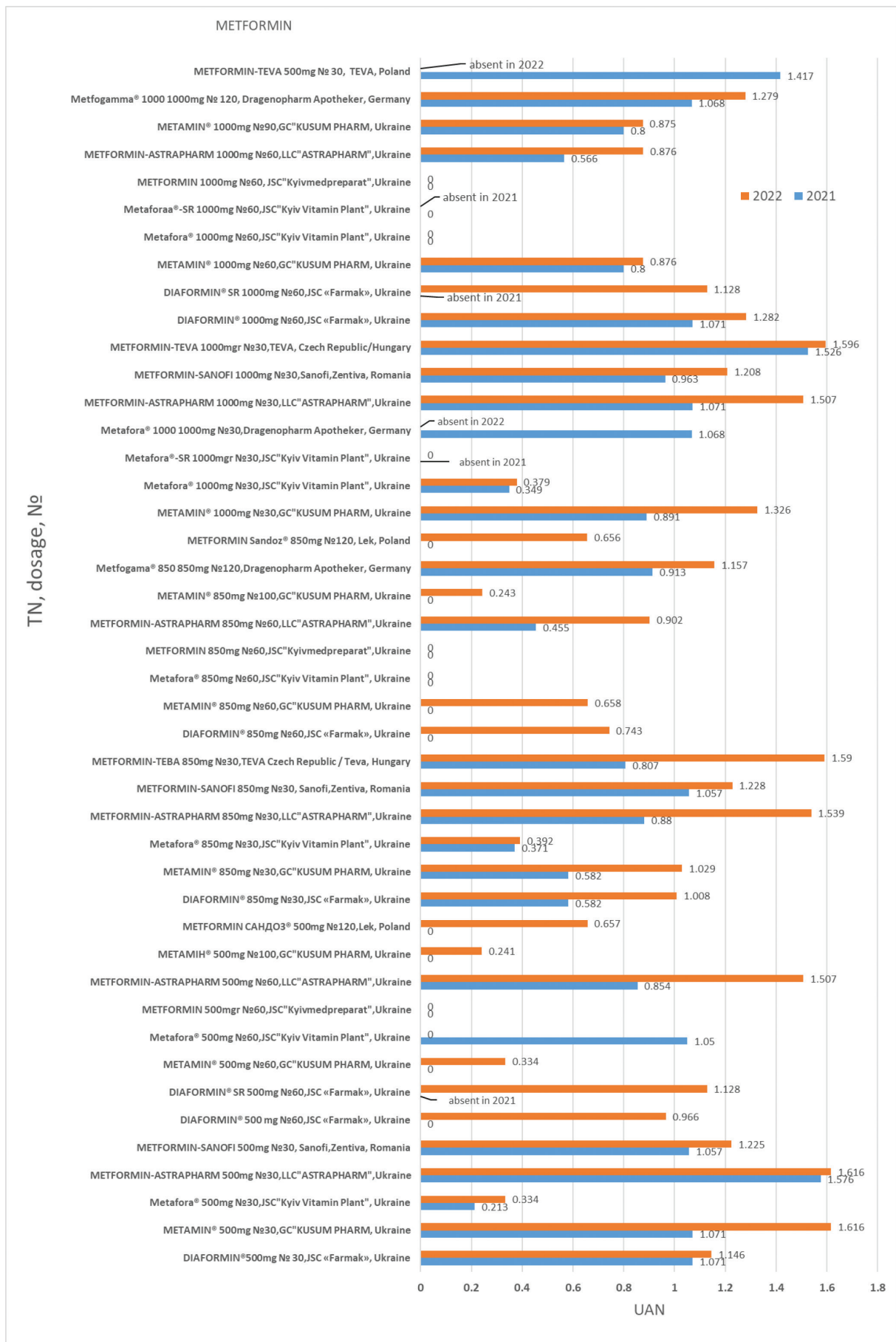


Figure 6. Dynamics of the amount of co-payment for DDD of metformin drugs (UAH) for 2021–2022.

Conclusions

Sense beginning of humanitarian crisis in Ukraine, the reimbursement system is experiencing negative changes: an increase in drug prices, the amount of patient copayments, and a decrease in the number of GLDs that are subject to full reimbursement. But in same time despite the fact that Ukraine is suffering from military actions, the state managed not only to maintain the functioning of the reimbursement system, but also to introduce positive changes

in the reimbursement of drugs – to increase the number of GLDs that are subject to full compensation and including extended dosage forms. This shows that the healthcare system in Ukraine is quite stable, but at the same time, it is necessary to note the Ukraine got great support from international governments and community. Future models should take a health system strengthening approach, use patient-centred design, and should be co-created with patients and providers.

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