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- ❑ РЕЗУЛЬТАТЫ РОССИЙСКИХ
ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

PHARMACOECONOMIC ANALYSIS OF THE USE OF A FIXED DOSE COMBINATION OF METFORMIN AND GLIBENCLAMIDE IN THE THERAPY OF DIABETES MELLITUS TYPE 2

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Abstract

Retrospective analysis of using fixed combinations of metformine and glibenclamide against separate scheme was carried out using the following methods: "cost-effectiveness", "budget impact" and "sensitivity analysis". For assessment of long-term impact of the compared methods of therapy on the results of the cost-effectiveness analysis, in terms of QALYs, and cost analysis, a Markov model with a 20-year model horizon was used. The compared alternatives were a fixed dose combination (FDC) of metformin and glibenclamide (Glucovance) and non-fixed dose combinations (nFDC) of glibenclamide (Maninil) and each of the three generics of metformin, consumption of which took a leading position in consumption in the Russian Federation (Siofor, Metformin-Richter and Formetine).

The effectiveness analysis showed that the total QALY for 20 years made 6.7121 and 6.2416 for the therapy with metformin FDC and nFDC respectively. And the cumulative cost made 2,512 thousand roubles, 2,687 thousand roubles, 2,690 thousand roubles and 2,696 thousand roubles for the therapy with Glucovance and combinations of Maninil and Formetine, Metformin-Richter and Siofor respectively.

Conclusion: Therapy with Glucovance is a preferred alternative compared to the use of non-fixed dose combinations of Glibenclamide and Metformin, as it is the most cost-effective and ensures a better quality of life of patients in the long run.

Key Words: Diabetes mellitus type 2, QALY, CER, cost-effectiveness analysis, metformin, glibenclamide, Glucovance.

Introduction

Diabetes mellitus (DM) is a non-contagious epidemic, which is one of the most dangerous challenges for the whole mankind in the 21st century. According to the International Diabetes Federation (IDF), in 2013 there were about 382 million people suffering from DM in the world, and according to the WHO projections this number will reach 592 million people by the year 2035 [2]. Complications of diabetes, including cardiovascular diseases, caused 4.8 million deaths in the year 2012 [3]. And patients with DM type 2 make 85 – 90%. According to the National Registry of Patients with DM, as of the year 2014, in the Russian Federation the incidence of outpatient visits is 4.145 million people, more than 3.7 million of them are patients with DM type 2 [31], however, according to the results of epidemiological studies, the actual number of patients with DM type 2 may be 3 – 4 times higher in our country [4]. According to the Ministry of Healthcare of the Russian Federation, in the Russian Federation the mortality rate due to complications of DM makes 6.7 cases per 100,000 persons a year; disability due to DM occurs in 2.1 cases out of 100,000 persons a year [1,4]. According to the International Diabetes Federation (IDM), in the year 2010 the global costs for treatment and prevention of diabetes made more than 376 billion US dollars [2].

At the present time, development of a therapeutic approach to patients with DM type 2 is one of the most challenging and difficult tasks of modern medicine. A modern diabetes control strategy is focused on maximum effective prevention and control of progression of the disease and complications associated to it.

These facts show the importance of a pharmacoeconomic evaluation of pharmacotherapy of diabetes mellitus type 2 as an instrument of optimization of pharmaceutical help focused on reducing the risk of developing complications and improvement of quality of life.

Study Objectives and Tasks

The objective of this study was evaluation of clinical and economic effectiveness of Glucovance used in patients with inadequate glycemic control, compared to one of the three nFDC, each of which included glibenclamide and one of the generics of metformin, in the context of the Russian Federation.

In course of research development costs for pharmacotherapy were calculated with the chosen drug products for DM type 2 treatment and costs for medical services and value of costs of care of DM type 2 complications, taking into account their frequency for each of the compared schemes. The obtained data used for conducting of the pharmacoeconomic analysis "cost-effectiveness" taking into account quality of life patients and for conducting of "budget impact analysis". "Sensitivity analysis" based on variability of daily doses in favor for alternative generics in compare with fixed combination and used as an examination for stability of calculated results.

Comparator Drugs

A fixed dose combination of metformin was presented by Glucovance. Formulation of non-fixed dose combinations was obtained on the basis of the performed consumption analysis. Based on the pharmaceutical market monitoring data, three generic drugs, Siofor, Formetine and Metformin-Richter, taking the largest market share in the year 2015 according to the IMS, were chosen as the most relevant alternatives containing metformin active substance as a monocomponent.

Among the drug products containing glibenclamide as a monocomponent it was Maninil which accounted for more than 99% of consumption during the same period.

Thus, the compared alternatives were performed by the following regimens:

- Glucovance
- Siofor + Maninil
- Formetine + Maninil
- Metformin-Richter + Maninil

Materials and methods

This was a retrospective study, and a number of pharmacoeconomic analyses: "cost-effectiveness", "budget impact" and "sensitivity analysis" were performed according to the standard procedure.

For forecasting the long-term impact of the compared methods of therapy on the disease progression and presenting the results in additional quality-adjusted life years (QALY) there was used a probabilistic Markov model developed in Microsoft Excel with a 20-year model horizon and a discount rate of 3%.

The duration of a modelling cycle used in the cost-effectiveness analysis was 1 year (Figure 1). To obtain primary data for modelling in the “cost-effectiveness” analysis, based on the randomized clinical trial (RCT) data, the impact of the compared treatment regimens on the glycated hemoglobin level (HbA1c%) was evaluated. Then the impact of variation of the HbA1c% level on the frequency of microvascular and macrovascular complications related to DM type 2 was predicted. At the final stage of the utility evaluation of the compared treatment regimens, there was performed calculation of additional quality-adjusted life years (QALY) for the whole model horizon, taking into account the impact of DM type 2 complications and their consequences.

Impact on Complications

UKPDS (The United Kingdom Prospective Diabetes Study) data were used to assess the impact of study endpoints used in the effectiveness analysis on a prognosis for DM type 2 complications.

In “Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study” (the average duration of observation: 10 years) 4,585 patients were involved in the assessment of risk reduction associated with a decrease of the average HbA1c by 1% with confounding factors at diagnosis of diabetes mellitus taken into account. Primary endpoints were death due to diabetes or death of other causes. Secondary endpoints were associated with development of myocardial infarction, stroke, amputation and microvascular complications (predominantly retinopathies), as well as cardiac insufficiency and cataract [13].

Figure 1 Markov model structure used for the cost-effectiveness analysis

Effectiveness Analysis

During the information search for effectiveness evaluation of the compared treatment regimens there was found a study where comparison of therapies with FDC and nFDC of metformin and glibenclamide was performed based on their impact on the patients' adherence to the therapy and indirectly on the ability to reduce the glycated hemoglobin level. In the retrospective observational study performed by L. Blonde, J. Wogen, C. Kreilik et. al. “Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin” there were evaluated the data of drug prescription and laboratory diagnostics of 1421 patients whose treatment with fixed and non-fixed dose combinations of metformin and glibenclamide first started in from August 2000 to July 2001. The population included patients with available data of the basic glycated hemoglobin level and of this level for 76 – 194 days of the combined therapy. Variation of the glycated hemoglobin level was examined using statistical regression for elimination of discrepancies between results. Additionally adherence to each type of combination therapy was examined. In the FDC group consisting of 950 patients there was observed a greater reduction of the HbA1c level than in the nFDC group (2.02% vs. 1.49%). In the FDC group there was also observed better adherence to the therapy than that in the nFDC group (84% vs. 76%). And the average daily doses of metformin and glibenclamide in FDC made 6 mg and 893 mg, and in nFDC 10 mg and 1291 mg respectively. Thus the study showed that the use of FDC of metformin and glibenclamide provided better control of the glucose profile with a lower daily dose than nFDC. [7]

The results of UKPDS 35 and the average frequency of endpoints with basic patient characteristics similar to those observed in the studies and described in the effectiveness analysis are presented in Table 1.

Apart from the UKPDS data, in this study there were used reduced risk rates of ischemic heart disease (IHD) and angina associated with the decrease of HbA_{1c} level by 1%, presented in Khaw KT et al.'s study (n=10,232; 2.4% with DM), making 23% and 14% respectively [15]. There was an assumption made that the initial average incidence of IHD and angina with the average HbA_{1c} level of 8.0% and the average age of 54 were equal to 30 events per 1,000 patient-years (similar to the incidence of myocardial infarction).

Table 1. Frequency of DM type 2 complications

Event:	ukpds 35	ukpds 35
	Risk reduction in case of decrease of the HbA1c level by 1%	Events per 1000 patient-years*
Death due to diabetes	21%	23.5
Death of other causes	14%	8.3
Stroke	12%	7.4
Myocardial infarction	14%	30
Cardiac insufficiency	16%	4.4
Amputation	43%	4
Microvascular complications	37%	22.8
Cataract	19%	6.9

* - with the average HbA1c level of 8.0% and the average age of 54, with the average duration of observation of 10 years.

QALY evaluation

For calculation of the total QALY over the whole model horizon there were used utility indices for each state of health in which a patient remains for some time. Differences in utility indices are caused by the development of diabetes mellitus complications in patients and change of their body weight.

The initial QALY value for patients with DM type 2 without serious microvascular and macrovascular complications prior to their enrollment to the study was taken as 0.82 according to the "Using the EQ-5D index score as a predictor of outcomes in patients with type 2 diabetes" study (n = 738) [17]. In the year of the event QALY was reduced by the given value in case of a complication. Most of complications were characterized by some loss of QALY in each year following the complication (Table 2). In the event of death the QALY value went down to "0" from the year of the beginning of the event till the end of the modelling period. Loss of body weight meant an increase in QALY in the year of the event.

As an example let us make calculation of QALY for a patient who suffered a stroke during the second year of the therapy with the model horizon of ten years. During the first year of the therapy the QALY value was 0.82. During the second year due to the stroke suffered the QALY value reduced by 0.164 and was equal to 0.656. Each of the following years modeled because of the stroke suffered during the second year meant the loss of 0.04 of the initial level which made 0.78 QALY. Thus, the quality of life of the patient for ten years was equal to $0.82 + 0.656 + 0.78 \cdot 8 = 7.716$ QALY.

Table 2. Utility values in the model

State	Impact on QALY (reduction of utility)
Stroke	-0.164 ^a
Stroke (the following years)	-0.04 ^b
Myocardial infarction	-0.055 ^a
Myocardial infarction (the following years)	-0.012 ^c
Angina	0.041 ^b
Angina (the following years)	-0.024 ^b
Cardiac insufficiency	-0.108 ^a
Cardiac insufficiency (the following years)	-0.018 ^c
IHD	-0.09 ^a
Amputation	-0.28 ^a
Microvascular complications	-0.0252 ^d
Cataract	-0.017 ^b
Blindness (one eye)	-0.074 ^a

a – according to "Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62)" study [18];

b – according to "Cost-effectiveness of insulin analogues for diabetes mellitus" pharmacoeconomic study [19];

c – based on the materials of "Methods for the economic evaluation of health care programs" [16];

d – used an average rate of utility decreasing in case of renal insufficiency (-0,0263) from "A model to estimate the lifetime health outcomes of patients with type 2 diabetes: UKPDS Outcomes Model (UKPDS 68)", and in case of neuropathy (-0,024) from the pharmacoeconomic study "Cost-effectiveness of insulin analogues for diabetes mellitus" [10];

RESULTS**Cost Analysis**

The cost analysis was presented by calculation of medical costs for the therapy of DM type 2, for each of the compared regimens (costs for comparator therapy and costs for medical procedures according to the standard of medical care for patients with DM type 2), and costs for complications of DM type 2.

The used information about the drug dosage regimens was taken from the study, on the basis of which the effectiveness analysis was performed [7], and it complied with the standard of primary medical care in non-insulin-dependent diabetes (outpatient) d/d January 18th, 2013, and with the instructions for use of medications [9]. The cost of drug products was calculated based on the maximum sale prices set by manufacturers for medicines on the list of vital and essential drugs or, in the absence of a drug product in the list, based on IMS wholesale prices.

Calculation of the cost of treatment with drugs found in the compared regimens for a year of therapy is presented in Table 3.

Table 3. The results of calculation of the average cost of a year of treatment with drugs included into the compared therapy regimens

COST OF THERAPY	COST OF ONE DAY OF TREATMENT	COST OF ONE YEAR OF TREATMENT
GLUCOVANCE	16,6 ₺	6 059,00 ₺
MANINIL	2,95 ₺	1 077,73 ₺
FORMETINE	2,85 ₺	1 041,80 ₺
METFORMIN-RIECHTER	3,48 ₺	1 271,80 ₺
SIOFOR	5,18 ₺	1 889,06 ₺

The next step was to calculate the costs for medical procedures including the data on the quantity and the cost of health resources according to the standard of primary medical care in non-insulin-dependent diabetes (outpatient) d/d January 18th, 2013. The prices for medical services were taken from tariffs of the Moscow Federal Compulsory Medical Insurance Fund (as of the year 2015) [11]. The total cost of diagnostic procedures according to the standard made 76,220 roubles per patient.

Calculation of costs in case of complications of diabetes was based on the data from Russia (I. I. Dedov, 2010) (Table 4) [12].

Table 4. Costs in case of complications of DM

State of health / adverse event	Costs, RUB	
	The first year	The following year
Stroke	307 446	23 532
Myocardial infarction	417 027	259 575
Blindness	48 404	-
Angina	260 552	259 575
Cardiac insufficiency	27 946	27 840
Amputation	450 996	-
Cataract	27 000	-
Other microvascular complications (neuropathy, nephropathy)	522 789	55 610

Cost-Effectiveness Analysis

On the final stage of the cost analysis total costs for DM type 2 management in the model horizon of 20 years were calculated. Costs included costs for comparator therapy and the costs for medical services according to the standard of medical care for patients with DM type 2 of the Ministry of Healthcare of the Russian Federation. Costs for complications of DM type 2 were also calculated. Results of the cost analysis are presented in Table 6.

An intermediate result of the effectiveness analysis was evaluation of the impact of the use of FDC and nFDC of glibenclamide and metformin on the frequency of complications of DM type 2. (Table 5).

Table 5. Results of evaluation of the impact of the use of FDC and nFDC of glibenclamide and metformin in 10,000 patients on the frequency of complications. The results are presented as variation of the number of episodes of complications within 20 years.

Complication	FDC compared to nFDC (additional prevented cases)
Stroke	94
Myocardial infarction	445
Blindness	447
Angina	445
IHD	731
Cardiac insufficiency	75
Amputation	182
Microvascular complications	894
Cataract	139
Death from diabetes	523
Death of other causes	123

Then for evaluation of the utility of treatment regimens, the calculated number of complications for the compared regimens, with their consequences taken into account, was brought to a single validated index – QALY (Table 6). BMI values of patients and frequency of adverse events in the therapy with the compared drugs also had their impact on the QALY value.

The cost-effectiveness ratio was calculated using the following formula:

$$CER = \text{Cost/QALY, where}$$

CER: cost-effectiveness ratio

Cost: total cost for the compared therapy regimen, RUB

QALY: incremental effectiveness rate which indicates quality-adjusted life years.

Thus, therapy with Glucovance demonstrated the highest utility value (in QALY terms) with the least cumulative costs per patient compared to non-fixed dose combinations.

Budget Impact Analysis

In the course of the budget impact analysis there were found financial consequences of the increase of the number of patients taking Glucovance for the subsequent year. There were evaluated only cost components including costs for drug products, medical services according to the standard of medical care for patients with DM type 2 of the Ministry of Healthcare of the Russian Federation and costs for complications of DM type 2.

For illustrative presentation of results of the analysis, there was calculated an economic effect gained for 20 years as a result of crossover of a nominal cohort of 100 patients from the given drug products to Glucovance (Table

7). There were evaluated only cost components including costs for drug products, medical services according to the standard of medical care for patients with DM type 2 of the Ministry of Healthcare of the Russian Federation and costs for complications of DM type 2. Thus, the cost components reflect the expenses directly accounted for healthcare.

Table 7. Settings for the ratio of the use of comparator drugs Values for the current year are obtained on the basis of market shares in packages of the compared products in 2015, according to the IMS.

Treatment regimen	Percentage of patients receiving treatment in the current year (%)	Percentage of patients receiving treatment during the planned years (%)
Glucovance	6	100
Formetine + Maninil	29	0
Metformin Richter + Maninil	17	0
Siofor+ Maninil	48	0

The total cost for the therapy under the specified above terms made 268,142,300 RUB with the current percentage ratio of the use of drug products, and 251,232,827 RUB with the planned ratio. Similarly, costs for drug products only made 3,141,314 RUB and 6,793,505 in the current period and in the planned period respectively.

As a result of the performed budget impact analysis it was found that the increase of the percentage of patients taking Glucovance for the therapy of DM type 2 would lead to saving of 16,909,474 for the period of 20 years (on average, 845,474 RUB a year) for the nominal cohort of 100 patients.

The results of budget impact analysis in terms of costs for drug products and total costs for the therapy of DM type 2 with each of the compared regimens are presented in Figures 2 and 3 respectively.

Sensitivity analysis

A sensitivity analysis was performed to assess the impact of uncertain variables on reliability of results of modelling. Contrary to the common practice for Russia, variables for the cost of comparator drugs did not have the highest model uncertainty. This happened because the share of costs for drug products was comparatively small in the whole structure of costs, and the probability of a radical change in prices of the drug products from the list of vital and essential drugs was not high. A one-way sensitivity analysis based on variation of a parameter with the highest probability of variation was performed [6].

Dosage of the comparator drugs was a varying factor of the analysis. For performance of the cost analysis, information about the drug dosage regimens was taken from the same cohort study on the basis of which the effectiveness analysis was performed. According to this study, the described effectiveness level was achieved with the following average daily doses: a fixed dose combination – 6 mg of glibenclamide and 893 mg of metformin; non-fixed dose combination – 10 mg of glibenclamide and 1297 mg of metformin. In this study an assumption was made in favour of non-fixed dose combinations, and the average daily dose of metformin for calculation of costs was equated to 900 mg for all comparators. Average daily doses of glibenclamide for fixed and non-fixed dose combinations were 6 and 10 mg respectively.

However, as there were no data showing variation of the effectiveness ratio of the compared regimens when using equal daily doses, the results were evaluated by a sensitivity analysis. The Table 8 presents the study results

Table 6. Results of cost-effectiveness analysis. Model horizon: 20 years. Discount rate: 3%. Calculated per 1 person.

Costs\Therapy regimens	Glucovance	Formetine+ Maninil	Metformin-Richter + Maninil	Siofor + Maninil
Cost of DM type 2 therapy RUB	911 309	867 138	869 717	876 638
Cost of DM type 2 complications therapy RUB	1 601 020	1 819 761	1 819 761	1 819 761
Cumulative costs, RUB	2 512 328	2 686 899	2 689 478	2 696 399
QALY	6,71211	6,24156	6,24156	6,24156
CER	374 298	430 485	430 898	432 007

Costs for drug products in the budget impact analysis

Figure 2. Impact on costs (roubles) for drug products depending on variation of the percentage of patients using different treatment regimens

Total costs for treatment regimens in the budget impact analysis

Figure 3. Impact on total costs depending on variation of the percentage of patients using different treatment regimens

evaluated by a single-way sensitivity analysis representing the following scenario: for a fixed dose combination and for all non-fixed ones, the average daily dose of glibenclamide was taken as 10 mg, and the dose of metformin was taken as 1500 mg. The effectiveness results for the compared regimens remained unchanged.

The sensitivity analysis showed that the results of the study tolerated variation of the average dosage of Glucovance by 70% with the dosage of Maninil being unchanged, which indicates to a high degree of reliability of the results of the modelling.

Conclusions

Standard pharmacoeconomic methods, such as “cost-effectiveness”, “budget impact” and “sensitivity analysis”, were used in this study. The literature survey and the effectiveness analysis performed as a part of the study showed that the use of Glucovance was associated with a better control of the glucose profile of a patient which reduced the frequency of DM type 2 complications in the long run. These factors were indirectly presented as an integrated effectiveness value – QALY, which included both the quantity and the quality of a patient’s life depending on the frequency of complications, the BMI and adverse events of the therapy. The QALY for Glucovance made

Table 8. Cost-effectiveness results evaluated by a sensitivity analysis

Compared treatment regimens	Glucovance	Maninil + Formetine	Maninil + Metformin-Richter	Maninil + Siofor
Cost of DM type 2 therapy	918,402 RUB	874,926 RUB	879,224 RUB	890,758 RUB
Cost of DM type 2 complications therapy	1,601,019 RUB	1,819,760 RUB	1,819,760 RUB	1,819,760 RUB
Cumulative costs	2,519,421 RUB	2,694,686 RUB	2,698,984 RUB	2,710,519 RUB
CER	375,354	431,732	432,421	434,269

6.7121. The QALY for drug products of non-fixed dose combinations of metformin and glibenclamide made 6.2416 for the whole modelling period.

The cost analysis showed that the lowest cumulative costs were related to the use of Glucovance (2,512 thousand roubles), which was mainly due to the reduction of expenses for complications of DM type 2 when using a fixed dose combination. And the cumulative costs for the therapy with nFDC of Maninil and Formetine, Metformin-Richter and Siofor made 2,687 thousand roubles, 2,690 thousand roubles, 2,696 thousand roubles respectively.

The therapy with FDC of metformin and glibenclamide (Glucovance), compared to nFDC of Maninil and Formetine, Metformin-Richter and Siofor, is a dominant method, as it is associated with better effectiveness and lower cost. The performed sensitivity analysis showed that, even in case of increase of the average daily dose of Glucovance by 70% compared to the values initially specified in the study, the use of FDC would ensure a higher QALY level with lower cumulative costs; and the use of Glucovance reduced the costs in the healthcare due to reduction of frequency of DM type 2 complications and consequently the expenses for them.

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