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- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ АНАЛИЗА "ВЛИЯНИЯ НА БЮДЖЕТ"
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

PHARMACOECONOMIC ANALYSIS OF RYZODEG®, A COMBINATION OF SOLUBLE ULTRA-LONG-ACTING HUMAN INSULIN ANALOGUE (INSULIN DEGLUDEC) AND ULTRA-SHORT INSULIN ANALOGUE (INSULIN ASPART), USE IN THERAPY OF TYPE 2 DIABETES

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Abstract:

Title: *"Pharmacoeconomic Analysis of Ryzodeg®, a Combination of Soluble Ultra-long-acting Human Insulin Analogue (Insulin Degludec) and Ultra-short Insulin Analogue (Insulin Aspart), Use in Therapy of Type 2 Diabetes"*

Study objective: *The objective of this study was to evaluate, whether the use of the combination of basal ultra-long insulin (degludec) and ultra-short insulin (aspart) in the ratio of 70% and 30% in one injection is pharmacoeconomically justified choice for insulin therapy with basal and prandial components for type 2 diabetes mellitus patients with insufficient glycemic control, treated with maximum tolerated doses of metformin in monotherapy.*

Materials and methods: *Study design – retrospective, modeling. Methods of pharmacoeconomic analysis used are "cost-effectiveness" ("cost–utility"). The modeling horizon was 10 years; the discounting rate was 3%. Alternative comparators included combination of insulin degludec/insulin aspart (Ryzodeg®) and biphasic insulin aspart (NovoMix® 30).*

Results: *Calculated ICUR ratio showed that incremental cost of 1 additional QALY gained as a result of switching from NovoMix® 30 therapy to Ryzodeg® in addition to metformin therapy equals 519,896 rub. Comparing ICUR with WPS in the RF it can be concluded that Ryzodeg® insulin use is clinico-economically effective in comparison with biphasic insulin aspart. Pharmacoeconomic benefit of Ryzodeg® insulin reflects clinical superiority of the new insulin over the conventional biphasic insulin analogue: possibility to achieve control with a significantly better safety profile, a lower dose of insulin, less pronounced body weight changes and a flexible dosage regimen.*

Key words: *type 2 diabetes mellitus, QALY, CUR, "cost-utility" analysis, insulin degludec, insulin aspart, metformin*

Introduction

Diabetes mellitus (DM) is a metabolic disease with high prevalence and vigorous growth in the number of new cases, and one of the most dangerous challenges to the humankind in the XXI century. According to International Diabetes Federation (IDF), in 2014 there were around 387 million people suffering from DM worldwide, and according to WHO estimations, this number will increase by 205 million by 2035. DM accounted for 4.9 million deaths in 2014. According to the data of the State Registry of DM patients, by January 2013 3.779 million people were seeking help in healthcare facilities. Meanwhile the results of the control epidemiological studies conducted by the FSBI Endocrinology Research Center (ERC) of the Ministry of Health of the Russian Federation during the period from 2002 to 2010 showed that in fact number of patients with DM in Russia is about 3-4 times higher than officially registered reaching 9-10 million people, which accounts for around 7 % of the total population [1].

The development of therapeutic strategy for type 2 DM patients is currently one of the most important and serious challenges of the modern medicine. Current anti-diabetes strategy focuses on the most effective prevention and control of disease progression, as well as associated risks and complication treatment costs.

Current approaches to type 2 DM insulin therapy

Insulin therapy is the only pathogenically justified method of type 1 DM treatment and the most effective way to achieve glycemic control with underlying type 2 DM progression, when it is not achieved with oral antihyperglycemic medications (OAM) and/or glucagon-like peptide-1 agonists [1]. Moreover, according to most current type 2 diabetes treatment guidelines, in order to achieve the target glycemic levels more rapidly it is recommended to start insulin therapy as early as possible [3-5]. In addition a justified early beginning of insulin therapy with achievement of individual glycemic control targets is beneficial in terms of DM outcomes and long-term prognosis [6]. Nevertheless, adverse effects of intensive hypoglycemic therapy (including insulin), such as hypoglycemia (especially severe and nocturnal episodes), complexity and insufficient flexibility of the regimen, significantly complicate adequate insulin therapy intensification and optimization and limit potential of achievement the target goals [47, 48].

Insulin analogues have been available for clinical use since late 1990s. The main reason for the insulin analogue development was inconsistency of the human insulin kinetics after subcutaneous injections with the endogenous profile [30]. The primary attention during the development of the first basal insulin analogues was paid to the absorption rate from the injection site to

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achieve a more constant flat kinetic profile, and stronger molecular self-association than in human insulin. Different mechanisms are employed to prolong the action of the forms of basal insulin currently available for clinical use: low-soluble insulin-protamine (NPH insulin), pH-dependent precipitation (insulin glargine) and albumin binding (insulin detemir) [31]. However, in spite of increased absorption rate and improved PK parameters none of the existing basal insulin analogues (insulin glargine and insulin detemir) has an optimal kinetic profile without peaks, or is void of daily variability of action, which may influence the glycemic control, contribute to hypoglycemia development and also necessitate two injections daily in some patients [30,32,33]. Achieving a truly stable 24-hour basal level of insulinaemia was only an idea up to today.

Insulin degludec is the first basal insulin analogue with an ultra-long duration of action developed by Novo Nordisk. Insulin degludec molecules are capable of self-associating on the administration site forming multihexamers [34]. As a result of slow Zn release and hexamer dissociation, insulin degludec is very slowly absorbed into the systemic circulation.That is why measurable insulin degludec serum concentration is maintained for minimum 120 hours, and half-life period is more than 24 hours following subcutaneous administration [35]. In addition, after steady-state is achieved, serum concentration of insulin degludec administered once daily remains stable for 24 hours.

As a result, insulin degludec has a flat PD profile both in type 1 DM patients and type 2 DM patients [35, 36].

Thus, insulin degludec is a new generation of analogues - ultra-long-acting (more than 42 hours) insulin analogue with flat and stable PK and PD profile, which is non-inferior compared to clinically approved basal insulin (insulin glargine) analogues in terms of glycemic control improvement, with much rarer hypoglycemia cases (especially nocturnal)[40].

Glycemic profile control, which is achieved by the use of long-acting insulin, does not always meet the needs due to glucose level fluctuations in blood after meal. That is why insulin therapy starts not only with basal insulins, but also include a combination of long-acting and short-acting insulins, and also biphasic insulins which help control both basal and postprandial glycaemia. When necessary, therapy regimen can be easily intensified by adding an extra injection of postprandial insulin [3]. The start of insulin therapy is often impeded with complex therapy regimens and a combination of insulins and biphasic insulins help to overcome this problem. One of the widely used biphasic insulin analogue, NovoMix® 30 consisting of 30% insulin aspart dissolved for maintaining postprandial insulinaemia by its fast and short action mode and 70% insulin aspart protamine crystals for imitation of basal secretion by sustained release. In the 21st century biphasic insulin analogues are replaced with insulins of a new generation. Ryzodeg® is the first unique insulin product containing basal ultra-long-acting insulin analogue degludec and ultra-short prandial insulin aspart. Basal (insulin degludec) and prandial (insulin aspart) components of Ryzodeg® insulin do not interact with each other in the solution, and their combination does not affect pharmacokinetic and pharmacodynamic profiles of both insulins, but at the same time make time-action profile maximally close to physiological profile of endogenic insulin. Clinical studies of insulin degludec/insulin aspart in patients with type 1 and 2 DM showed that the new combination of insulin can significantly improve glycemic control at a lower risk of glycemia, especially nocturnal episodes, as compared to other clinically available preliminary mixed biphasic insulins (NovoMix® 30) [43]. Thus, in insulin-naïve patients with type 2 DM Ryzodeg® insulin therapy was associated with clinically and statistically significant lower frequency of confirmed and nocturnal confirmed hypoglycemic episodes (54% and 75% respectively; p<0.001) as compared to NovoMix® 30 [44].

Also, the use of insulin degludec/insulin aspart twice daily in patients with type 2 DM was beneficial in terms of hypoglycemia risk, and in cases of therapy intensification as compared to both basal insulin glargine and NovoMix® 30: the rate of overall confirmed and nocturnal confirmed hypoglycemic episodes was respectively 43% and 20% lower in patients who previously received basal insulin therapy, and correspondingly 32% and 73% lower in patients who previously received biphasic insulins [47]. The introduction of insulin degludec/insulin aspart (Ryzodeg®) to clinical practice makes it possible to overcome the existing limitations of the conventional biphasic insulin therapies and improves the chances of individual insulin therapy to achieve more tight and stable glycemic control (particularly concerning fasting glycaemia) in type 1 and 2 DM patients with a substantially better safety profile, allows more flexible administration depending on the clinical conditions (administration once or twice daily regardless of the time of day with any main meal), significantly reduces the number of injections and insulin doses, improves patients' well-being and treatment satisfaction as compared to conventional insulin analogues [43].

Purpose and objectives

The purpose of the study was to evaluate whether Ryzodeg® insulin is pharmacoeconomically justified choice for insulin therapy including basal and prandial insulin components in type 2 diabetes mellitus patients with insufficient glycemic control, receiving monotherapy with maximum tolerated doses of metformin, taking into account current limitations of the conventional biphasic insulin therapy. The original drug products were used as comparators in the current study, since they were used in randomized clinical studies for efficacy analysis. Compared alternatives included following insulin analogues: combination of insulin degludec/insulin aspart (Ryzodeg®) and biphasic insulin aspart (NovoMix® 30).

The following objectives were set to achieve the study purpose:

1. To evaluate costs of pharmacotherapy with selected drug products for type DM treatment.
2. To evaluate direct medical costs
3. To evaluate efficacy and safety of the compared therapy approaches in terms of glycosylated hemoglobin level decrease and effect on the rate of hypoglycemic episodes and patient's body weight according to RCS data.
4. To evaluate indirect medical costs including disability costs.
5. To evaluate benefit in QALYs for the compared therapy approaches based on efficacy and safety data of the drug product from RCS.
6. To conduct pharmacoeconomic analysis by "costs-efficacy" method based on costs and quality of life data obtained.

Materials and Methods

Cost-utility analysis was performed using the model created in Microsoft Excel and used for estimation of the results in terms of QALYs. The modeling horizon was 10 years; the discounting rate was 3% [8-10]. The study included pharmacoeconomic evaluation of Ryzodeg® (insulin degludec/insulin aspart) as compared to NovoMix® 30 (biphasic insulin aspart) for treatment of adult patients (18 and older) with type 2 DM and insufficient glycemic control against OAM treatment and/or combined in single pharmaceutical form or separately, as well as basal insulin analogues.

Efficacy analysis

During the information search for efficacy of compared therapy regimens assessment, a number of clinical studies were selected, which compare the insulin analogues by their effect on glycosylated hemoglobin level lowering and safety predominantly related to the rate of hypoglycemic episodes and effects on body weight.

The meta-analysis described in the work of A. Vaag, J.S. Christiansen, L.K. Niskanen. «Lower rates of overall, nocturnal and severe hypoglycaemia during maintenance treatment with IDegAsp vs biphasic insulin aspart 30 in patients with type 2 diabetes mellitus: a meta-analysis», compared the combination of insulin degludec and dissoluble insulin aspart with biphasic insulin aspart 70/30. This meta-analysis included two 26-week studies of 868 patients. As anticipated, the treat-to-target study the target control of HbA1c was achieved using both drug products without statistically significant difference: 7.06% and 7.07% for combination of degludec/insulin aspart and biphasic insulin respectively. After the titration period the overall confirmed, nocturnal and severe hypoglycemic episodes were respectively by 31%, 62% and 84% lower for insulin degludec/insulin aspart combination as compared to biphasic insulin aspart. Besides, the use of Ryzodeg® insulin demonstrated an average of 0.5 kg less weight gain in patients as compared to biphasic insulin aspart. [11]

In this study basic values of hypoglycemic episodes rate expressed as the number of episodes per patient-year for NovoMix® 30 were obtained from the work «UK Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration», that described more than 5-year follow-up of patients receiving biphasic insulin aspart. The average frequency of non-severe and severe hypoglycemic episodes was 10.2 and 0.7 episodes per patient-year respectively. [12] The rate of hypoglycemic episodes for Ryzodeg® was obtained by comparing NovoMix® 30 data with the results of the above-mentioned comparative meta-analysis (table 1).

The work «Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management» showed that the frequency of blood glucose self-measurements increases on average by 6.2 tests a week after hypoglycemic episode. [13]. Data on the number of extra blood glucose tests for the compared alternatives were obtained by means of multiplying the rate of confirmed hypoglycemic episodes found in the analysis of RCS by 6.2. Then the value obtained for each of the compared regimens was added to the conventional number of tests equal for both drug products – 7 tests a week.

Consequently the number of blood glucose tests per patient a week was calculated according to the following formula:

$$R(SMBG) = R(Hypo)/52*6.2 + 7, \text{ where}$$

R(SMBG) – number of blood glucose self-measurements per patient a week;
R(Hypo) – total number of all confirmed hypoglycemic episodes per patient-year;
52 – number of weeks in a year;
6,2 – number of additional measurements a week after hypoglycemic episode;
7 – conventional number of tests without hypoglycemic episodes

This analysis includes the rate of hypoglycemic states registered during supportive therapy at which the target glycemic control was already achieved and daily dose of insulins was stabilized. The division of hypoglycemic episodes into severe and the daytime and nocturnal non-severe ones was connected with different levels of expenses and utility characteristic for these states. The work of Vaag et al. based on meta-analysis data described only the difference in the rate of overall confirmed, nocturnal and severe hypoglycemic episodes, without division of hypoglycemic episodes into daytime and nocturnal non-severe ones [11]. Separate values of the rate ratio of the daytime and nocturnal non-severe hypoglycemic episodes during supportive therapy for Ryzodeg® and NovoMix® 30 (0.76 and 0.39 correspondingly) were obtained by request of the authors of meta-analysis and refer to the unpublished data. The rate ratio of severe hypoglycemic episodes for Ryzodeg® and NovoMix® 30 was 0.16 according to the published data of meta-analysis [11].

The results of the efficacy analysis are presented in Table 1.

Table 1. Results of Efficacy Analysis.

Parameter	Ryzodeg®	NovoMix® 30	Data source	Ryzodeg®/ NovoMix® 30 hypoglycaemic episode rate ratio***
Rate of non-severe daytime hypoglycemic episodes, per patient-year	6,43	8,46**	*12, 47, 49	0.76
Rate of non-severe nocturnal hypoglycemic episodes, per patient-year	0,68	1,74**	*12, 47, 49	0.39
Rate of severe hypoglycemia episodes, per patient-year	0,11	0,7**	11, 12	0.16
Blood glucose measurement, per patient a week	7,8608	8,3	13	-
Weight gain, kg	1,7	2,2	*11, 47, 49	-

* calculations are based on the data of UK Hypoglycaemia Study and meta-analysis of two RCS where the direct comparison of combination of insulin degludec/insulin aspart with biphasic insulin aspart was made [12, 49]
** the total events per patientyear are 0.7 for severe hypoglycemia and 10.2 for non-severe hypoglycemia (UK Hypoglycaemia Study) [12]/. The division of all non-severe hypoglycaemic episodes into daytime (82.9%) and nocturnal (17.1%) ones is based on meta-analysis data.
*** Ryzodeg®/ NovoMix® 30 hypoglycaemic event rate ratio for the maintenance period according to the meta-analysis.

Utility evaluation

An integral parameter QALYs was used in the cost-utility analysis.

To calculate the overall QALYs for the total modeling period we used the utility indicators for each condition in which a patient finds himself during a certain period of time. Existence of different utility levels is determined by hypoglycemic episodes, weight gain and also by the necessity of frequent self-measurements of blood glucose using analyzer.

To estimate the overall quality of life of type 2 DM patients, and also the impact of the emerging complications, the values of benefits per year of treatment were used. Basic value of QALYs for the type 2 DM patients without serious micro- and macro-vascular complications before the enrollment, was considered to be 0.8 according to the data of the study "Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD)" [18]. Occurrence of hypoglycemic episodes of different severity as well as other conditions included in the model was accompanied by the certain decrease in QALYs (Table 1).

Table 2. Utility values in the model

Condition	Utility
Type 2 DM (basic utility values)	0.8[a]
Confirmed non-severe daytime hypoglycemic episode	-0.0041[b]
Non-severe nocturnal hypoglycemic episode	-0.0067[b]
Severe hypoglycemic episode	-0.0565[b]
Measurement of glucose level with analyzer	-0.0000221[c]
Weight gain by 1 kg	-0.001762115[d]

a – according to the data of the study "Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD)" [18]
b – according to the data of the study "Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries" (calculated per year) [19]
c – according to the data from the study "Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey." as calculated per year of weekly glucose measurements [20]
d – the use of utility value based on NICE clinical guidelines data on obesity for men with BMI 28-35 [14]

Cost analysis

Disease cost analysis was presented as a calculation of direct and indirect costs. The analysis of direct costs included comparator treatment costs, costs of blood glucose test-strips and costs of medical services. The analysis of indirect costs included disability costs [7].

Information about the dosing regimens and therapy regimens used by default is in accordance with the primary medical care standards for insulin-independent diabetes mellitus (outpatient) dated January 18, 2013, as well as patient information leaflets [26]. Ryzodeg® insulin doses were 16 % lower than biphasic insulin aspart doses, according to meta-analysis data [11.

Data on the comparator prices were obtained from VED Maximum Selling Price Registry [28].

The pharmaceutical therapy costs for all drugs were calculated according to the following formula:

$$C(1мг) = \frac{P(уп.)}{D \times N};$$

Where C (1mg) is the cost of 1 mg of the medicinal product (rub.);
P (pack) is the price of a pack;
D (dosage) is the amount of active ingredient in medicinal product unit (mg);
N is the number of medicinal product units per pack (pcs.)

Data on the calculation of mean cost of 1 mg of the drug products included in the compared therapy regimens are shown in Table 3.

Table 3. Data on the calculation of mean cost (rub.) of 1 mg of the drug products included in the compared therapy regimens

INN	Drug	Cost of a pack	IU/mg	Number per pack	Mean cost of 1 mg
Degludec/ aspart	Райзодег®	5940	300	5	3,96 р.
Biphasic aspart	НовоМикс 30®	1351,52	300	5	0,90 р.
metformin	Глюкофаж®	159	500	30	0,01 р.
		300	1000	30	

Once the cost of 1 unit was calculated, the daily dose of drug products was calculated according to the following formula:

$$C(PDD) = C(1mg) \times \overline{d(D_i)};$$

Where C (PDD) is the cost of a prescribed daily dose (rub.);
C (1 mg) is the cost of one medicinal product unit (rub.)
$\overline{d(D_i)}$ is the prescribed daily dose of the drug product (mg).

Results of the average annual therapy cost calculation with the drug products included in the treatment regimens compared are shown in Table 4.

Table 4. Results of the average annual therapy cost calculation with the drug products included in the treatment regimens compared.

Therapy cost	Daily dose	Daily treatment cost	Annual treatment cost
Ryzodeg®	50,4*	199,58 rub.	72 848,16 rub.
NovoMix® 30	60*	54,06 rub.	19 732,19 rub.
Glucophage®	2000	20,60 rub.	7 519,00 rub.

*difference in doses is 16% (according to meta-analysis data) [11]

Next, costs of medical services were evaluated including data on the number and cost of health resources as per PHC standard for insulin-independent diabetes mellitus (outpatient) dated January 18, 2013. Prices of medical services were obtained from the tariffs of Federal Compulsory Medical Insurance Fund (FCMIF) (as of the year 2014) [29]. It was assumed that the cost of a severe hypoglycemic episode is comprised of the cost of the emergency medical service (EMS) call, the cost of five bed days and the cost of a glucagon injection. The cost of a non-severe hypoglycemic episode was equaled to the cost of a glucose injection (22 rubles); also it was assumed that consultation of general practitioner (GP) was required in 5% of such episodes and consultation of endocrinologist in 4% of cases. The cost calculation of hypoglycemic episodes is shown in table 5. Data on prices of test-strips for the blood glucose level measurement with analyzer were obtained from the weighted average cost of the Moscow pharmacies [28].

The evaluation of indirect costs was based on the effect of every hypoglycemic episode on the number of disability hours. Results of the study «Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management" were used; they are shown in Table 6. [15] For severe hypoglycemic episodes disability was calculated on the basis of 7 lost working days.

Results

At the next stage of the analysis the overall costs of type 2 DM therapy were calculated for 10 years for each of the compared regimens, including the costs of the medicinal products, blood glucose level measurement and the costs associated with hypoglycemic episodes and medical services according to the type 2 DM treatment standards, and indirect costs associated with patient's disability. The structure of the costs is presented in Table 7 and Figure 1.

Table 6. Results of the analysis of indirect costs associated with disability as a result of every hypoglycemic episode

	Hypoglycemia during working hours	Hypoglycemia outside work	Nocturnal hypoglycemia
Rate of events (%) [15]	28,8	53,9	17,4
Rate of cases of lost working time (%) [15]	23,3	14,3	28,1
Lost working hours*	11,4	15,1	14,2
Costs per hour, rub.**	175	175	175
Costs of a hypoglycemic episode, rub.	464,8	377,8	698,2

*- in a 40-hour working week
**-with an average salary of 30,000 rub.

Table 7. Results of the cost analysis (modeling horizon – 10 years)

	Ryzodeg®	NovoMix® 30
Costs of treatment	794 735.06 rub.	263 575.38 rub.
Costs of hypoglycemic episodes	29 102.93 rub.	137 399.19 rub.
Test-strip costs	53 139.48 rub.	56 105.40 rub.
Indirect costs	70005.23	152438.76
Cumulative costs	1 804 341.25 rub.	1 474 136.87 rub.

The performed efficacy analysis showed that the highest efficacy value expressed in QALYs accounts for the combination of insulin degludec and insulin aspart.

QALY values for Ryzodeg® insulin and biphasic insulin aspart calculated with the modeling horizon of 10 years are shown on Table 8.

Table 8. Results of utility analysis (modeling horizon 10 years)

	Ryzodeg®	NovoMix® 30
QALY	7.5960	7.1006

Since the number of QALYs gained due to implementation of the therapy regimen, including insulin degludec, is higher than that of biphasic insulin aspart with higher cost values of insulin degludec, the ICUR (incremental cost-utility ratio) value reflecting the additional costs per 1 additional QALY gained by switching from one treatment method to another was calculated according to the formula:

$$ICUR = (Cost_1 - Cost_2) : (QALY_1 - QALY_2), \text{ where}$$

$Cost_1$, $Cost_2$ - overall costs
$QALY_1$, $QALY_2$ - utility from the medical interventions 1 and 2 respectively

Calculated for the 10-year modeling horizon ICUR ratio showed that the extra cost of 1 additional QALY gained due to Ryzodeg® therapy equals 519,896 rub. with a discounting rate of 3% compared with NovoMix® 30. The results of "cost-utility" analysis are presented in table 9. Calculated "will-

Table 5. Cost calculation of hypoglycemic episodes

Hypoglycemia	Manipulation	Cost, rub.	Number/rate	Cost per episode, rub.	Source
Severe	EMS call	4806	1	17734	FCMIF tariffs (Moscow)
	Hospitalization (bed-days)*	2433	5		FCMIF tariffs (Moscow)
	Glucagon injection	760	1		VED Selling Price Registry
Non-severe	Glucose injection	22	1	130	VED Selling Price Registry
	Consultation of GP	1200	0,05		FCMIF tariffs (Moscow)
	Consultation of endocrinologist	1200	0,04		FCMIF tariffs (Moscow)

*calculated per bed-day in medical ward and reanimation performance in 5% of cases

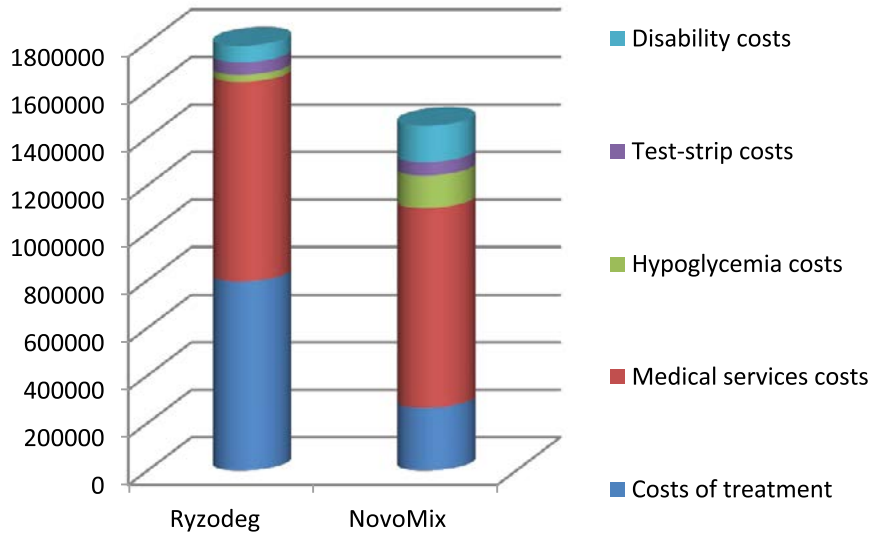

Figure 1. Cost structure (modeling horizon – 10 years)

ingness to pay threshold" (WPS) in the RF as of 2014 shows that if the value of ICUR ratio for 1 QALY is lower than 1,333,500 rub., then the alternative comparator is cost efficient [41]. Medical intervention with the ICUR value higher than the twofold WPS is unacceptable from the pharmacoeconomics perspective since it is associated with high costs [42].

Table 9. Results of "Cost-utility" analysis (modeling horizon – 10 years, discounting rate 3%)

Additional QALY	NovoMix
Ryzodeg	0,495482912
Additional costs	NovoMix
Ryzodeg	338843 rub.
ICUR	NovoMix
Ryzodeg	519 896 rub.

Thus, correlation of the ICUR calculated for the alternative comparators and WPS in the RF allows for the conclusion that the use of Ryzodeg® is cost efficient as compared with NovoMix® 30 from the pharmacoeconomics perspective.

References:

1. Clinical recommendations. Algorithms of specialized medical help for patients with diabetes mellitus, edited by I.I. Dedov, M.V. Shestakova, issue 6, 2013
2. International Diabetes Federation (IDF). Diabetes Atlas, Sixth Edition 2014 Update, Available at; htpp://www.idf.org/diabetesatlas/
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2015;38:140-149
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract. 2013;19:327-336.
5. Dedov I.I., Shestakova M.V., Ametov A.S., Antziferov M.B., Galstyan G.R. et al. Consensus of panel of experts of Russian Association of Endocrinologists for initiation and intensification of glucose lowing therapy in patients with type 2 diabetes mellitus. Diabetes Mellitus, 2011; 4:6-17
6. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care. 2004;27: 1028-1032.
7. Yagutina R.I., Kulikov A.Yu., Komarov I.A. Methodology of cost analysis during pharmacoeconomic studies //Pharmacoeconomics. Modern pharmacoeconomics and pharmacoepidemiology/ 2011. No. 3. P.3-6.
8. Yagutina R.I., Khabriev R.U., Pravdyuk N.G. Evaluation of healthcare technologies. M.: Medical Information Agency LLC, 2013. – 416 pp.
9. Khabriev R.U., Kulikov A.Yu., Arinina E.E. Methodological bases of pharmacoeconomic analysis. M.: Medicine, 2011. 128 pp.
10. Yagutina R.I., Kulikov A.Yu., Arinina E.E. Pharmacoeconomics of type 2 diabetes mellitus. M.: MIA, 2011. 352 pp.
11. A. Vaag, J.S. Christiansen, L.K. Niskanen. Lower rates of overall, nocturnal and severe hypoglycaemia durring mainttennannce treaatment with IDegAsp vs biphasic insulin aspart 30 in patients with type 2 diabetes mellittus: a meta-analysis. EASD 2013 (Oral presentation 187)
12. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007 Jun;50(6):1140-7.
13. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665-71
14. National Institute for Health and Clinical Excellence (NICE) Clinical Guideline CMmmary (2006) - CG43 Obesity: full guideline, section 6 - health economics. http://www.nice.org.uk/nicemedia/pdf/CG43FullGuideline6v.pdf
15. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665-71.
16. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321:405–412, 2000
17. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. Ann Intern Med 2004;141:413–20.
18. Zhang P1, Brown MB, Bilik D. Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD). Diabetes Care. 2012 Nov; 35
19. Evans M1, Khunti K, Mamdani M et.al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries, Health Qual Life Outcomes. 2013 Jun 3;11
20. Evans M, Jensen HH, Bøgelund M. Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey. J Med Econ. 2013 Nov;16
21. Patrick W. Sullivan, PhD and Vahram Ghushchyan, PhD. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. Med Decis Making. 2006; 26(4): 410–420.
22. Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the economic evaluation of health care programs. 3rd ed. Oxford (UK): Oxford University Press; 2005.
23. Clarke PM, Gray AM, Briggs A, Farmer AJ A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom

Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004 Oct;47(10):1747-59
24. NICE technology appraisal guidance 248. Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. February 2012
25. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ. 2008 May 24;336(7654):1177-80
26. Order of MH of the RF "Standard of medical help for patients with diabetes mellitus" dated January 18th 2013.
27. R. E. Ratner, S. C. L. Gough, C. Mathieu. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes, Obesity and Metabolism 15: 175–184, 2013
28. www.grls.rosminzdrav.ru/
29. http://ora.ffoms.ru/
30. Lindholm A. New insulins in the treatment of diabetes mellitus. Best Pract Res Clin Gastroenterol. 2002;16(3):475–92.
31. Havelund S, Plum A, Ribel U, Jonassen I, Volund A, Markussen J, Kurtzhals P. The mechanism of protraction of insulin detemir, a long-acting, acylated analogue of human insulin. Pharm Res. 2004;21:1498–504.
32. Heise T, Nosek L, Rønn BB, Endahl L, Heinemann L, Kapitza C, Draeger E. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004;53(6):1614–20.
33. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes Obes Metab. 2007;9(5):648–59.
34. Jonassen I, Havelund S, Hoeg-Jensen T et al. Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin. Pharm Res (2012) 29:2104–2114.
35. Heise T, Hövelmann U, Nosek L, Bottcher SG, Granhall C, Haahr H. Insulin degludec has a two-fold longer half-life and a more consistent pharmacokinetic profile than insulin glargine. Presented at: American Diabetes Association 71st Scientific Sessions. San Diego, CA, USA, 24–28 June 2011.
36. Heise T, Hermanski L, Nosek L et al. Insulin degludec: less pharmacodynamic variability than insulin glargine under steady state conditions. Diabetologia 53(Suppl. 1), S387 (2010).
37. Garber AJ, King AB, Francisco AMO, Endahl L, Hollander PA. Insulin degludec improves long-term glycemic control with less nocturnal hypoglycemia compared with insulin glargine: 1-year results from a randomized basal-bolus trial in people with Type 2 diabetes. Diabetes 60(Suppl. 1), A20 (2011).
38. Zinman B, Philis-Tsimikas A, Cariou B et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes. Diabetes Care. 2012; 35(12):2464-2471.
39. Meneghini L, Atkin SL, Bain S et al. Flexible once-daily dosing of insulin degludec does not compromise glycemic control or safety compared to insulin glargine given once daily at the same time each day in people with Type 2 diabetes. Presented at: American Diabetes Association 71st Scientific Sessions. San Diego, CA, USA, 24–28 June 2011.
40. M.V. Shestakova, 6th Diabetologic Congress, Collection of Abstracts, May 19-22nd 2013, p. 103-104
41. Yagudina R.I., Kulikov A.Yu., Nguen T. Determination of rapids "willingness to pay" threshold in Russia, European and CIS countries// Pharmacoeconomics. Modern pharmacoeconomics and pharmacoepidemiology/ - No. 1 – 2011. P.7-12
42. Yagudina R.I., Sorokovikov I.V. Methodology of cost-utility analysis during pharmacoeconomic studies// Pharmacoeconomics. Modern pharmacoeconomics and pharmacoepidemiology.- No. 2 – 2012. P.9-12
43. Dedov I.I., Shestakova M.V. Insulin degludec/ insulin aspart – first combination product of basal and meal-time insulin analogues.// Diabetes Mellitus – No.2 – 2014, submitted in print
44. Franek E, Haluzík M, Varžić SC et al. IDegAsp provides superior FPG control and reduced hypoglycaemia vs BIAsp 30 in insulin-naive adults with type 2 diabetes: a randomised phase 3 trial. Diabetologia 2014; 57(Suppl1):S380
45. Heise T, Tack CJ, Cuddihy R, Davidson J, Gouet D, Liebl A, et al. A new-generation ultra-long acting basal insulin with a bolus boost compared with insulin glargine in insulin-naive people with type 2 diabetes: a randomized, controlled trial. Diabetes Care. 2011;34(3):669–74.
46. Liebl A, Davidson J, Mersebach H, Dykiel P, Tack CJ, Heise T. A novel insulin combination of insulin degludec and insulin aspart achieves a more stable overnight glucose profile than insulin glargine: results from continuous glucose monitoring in a proof-of-concept trial. J Diabetes Sci Technol. 2013;7(5):1328–36.
47. Fulcher GR, Christiansen JS, Bantwal G, Polaszewska-Muszynska M, et al. on behalf of the BOOST: Intensify Premix I investigators. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial. Diabetes Care 2014; DOI: 10.2337/dc13-2908
48. Kulikov A.Yu., Novikov I.V. Pharmacoeconomic analysis of use of modern insulin analogues in the treatment of type 2 diabetes mellitus.// Pharmacoeconomics: theory and practice. Volume 2, No. 3, 2014. P. 62-71
49. Kaneko S, Chow F, Choi DS, Taneda S, Hirao K, Park Y, et al. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: A 26-week, randomised, treat-to-target trial. Diabetes Res Clin Pract. 2015 Jan;107(1):139-47.