Фармакоэкономика

теория и практика

www.pharmacoeconom.com

№3 Том2 2014

- О ВОЗМОЖНОСТЯХ СОВМЕЩЕНИЯ АНАЛИЗА «ВЛИЯНИЯ НА БЮДЖЕТ» И АНАЛИЗА «ЗАТРАТЫ-ЭФФЕКТИВНОСТЬ» - СОЗДАНИЕ «3D» ФАРМАКОЭКОНОМИЧЕСКОЙ МОДЕЛИ
- ФАРМАКОЭКОНОМИКА САХАРНОГО ДИАБЕТА, РАКА ПОЧКИ, ПОСТИНСУЛЬТНОЙ СПАСТИЧНОСТИ
- СОЦИАЛЬНЫЕ АСПЕКТЫ ТАБАКОКУРЕНИЯ

Pharmacoeconomics
theory and practice

PHARMACOECONOMIC ANALYSIS OF MODERN INSULIN ANALOGUES IN THE TREATMENT OF DIABETES MELLITUS TYPE 2

Kulikov A.Yu. [1], Novikov I.V. [2]

[1]Laboratory of pharmacoeconomic studies, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation
[2]Department of Medicinal Provision and Pharmacoeconomics, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation

Synopsis:
Study purpose: *To determine preferential medicinal products for the treatment of diabetes mellitus type 2 in terms of pharmacoeconomic analysis based on comparative cost and efficacy, safety and quality of life ratio between the modern insulin analogues.*

Materials and methods: *Study design – retrospective, modeling. Methods of pharmacoeconomic analysis - cost-effectiveness, cost-utility. Alternatives compared – insulin aspart (NovoRapid®), insulin lispro (Humalog®), insulin glulisine (Apidra®), premix insulin aspart 30/70 (NovoMix® 30), premix insulin lispro 25/75 (HumalogMix® 25), insulin detemir (Levemir®) and insulin glargine (Lantus®).*

Data sources: *efficacy – analysis of publications on clinical studies performed; medicinal product prices – registry of quoted prices for vital and essential medicines; cost of healthcare resources – outpatient and polyclinical assistance standards.*

Study results: *Among short-acting insulin analogues, CER value was 1091.84 rub.; 1133.55 rub. and 1175,27 rub. for NovoRapid®, Humalog® and Apidra®, respectively. Among premix insulin analogues, CER value was 1418.47 rub. for NovoMix® 30 and 1512.08 rub. for HumalogMix® 25. Among basal insulin analogues CER value was 2084.39 rub. for Levemir® and 2471.23 rub. – for Lantus®.*
Cost-utility analysis for NovoRapid®, Humalog®, Apidra®, NovoMix® 30, HumalogMix® 25, Levemir® and Lantus® CUR value was 84463.04 rub., 87689.69 rub., 90917.35 rub., 99573.21 rub., 106144.38 rub., 79269.45 rub. and 93981.16 rub. for 1 QALY, respectively. Therefore, in terms of cost-utility, when insulins were added to OAD treatment, NovoRapid® is the preferable drug because of the lowest CUR value. Among premix and basal insulin analogues, NovoMix® 30 and Levemir® were preferable drugs because of the lowest CUR values in their group.

Keywords: *diabetes mellitus type 2, HbA1c(%), QALY, CER, CUR, cost-efficacy analysis, cost-utility analysis, insulin analogues, metformin*

Introduction

Diabetes mellitus (DM) is a noninfectious endemic disease, one of the most dangerous human challenges in XXI century. According to International Diabetes Federation (IDF), about 371 million people in 2012 had DM globally and according to WHO forecasts, this rate will increase to 552 million people by 2030. DM complications including cardiovascular diseases accounted for 4.8 million lethal outcomes in 2012. At that proportion of subjects with type 2 DM is 85-90%. According to the State Register of the Russian Federation, the number of DM subjects in Russia in 2012 exceeds 3.5 million humans, out of them 3.2 million have type 2 DM, however, according to epidemiological data, the actual number of subjects with type 2 DM may be 3-4 times as high. According to the Ministry of Health and Social Development, DM complicated-related mortality is 6.7 cases per 100 thousand (9 478 cases); DM-associated disability is reported in 2.1 cases per 100 thousand (24 415 cases). According to IDF estimates, global cost for the treatment and prevention of DM in 2010 exceeded 376 billion US dollars. [1,2]
Choice of therapeutic approach for DM type 2 subjects is currently one of the most vital and complicated medical challenges these days. According to the current recommendations, approach to type 2 DM therapy suggests gradual switch from diet therapy and modification of the lifestyle to pharmacotherapy with glucose-lowering agents.
While oral glucose-lowering agents are conventionally used as first-line therapy in subjects with type 2 DM, large proportion of subjects require insulin administration to achieve optimal glycemic control at a certain stage of the disease. Nevertheless, addition of insulin to the treatment scheme may reduce flexibility in selection of meal time, increase blood glucose monitoring frequency and increase the risk of body weight gain and hypoglycemic episodes. According to numerous clinical studies, these values may vary for different insulin analogues (short-acting, two-phase, basal). National examination of population health status in the US demonstrated that 28% subjects with type 2 DM received insulin therapy (16% - insulin monotherapy, 12% - insulin combined with oral antidiabetic drugs (OAD) [3].
Published AACE and ACE Consensus specifically pointed out comparison of various drugs by the following statement: "Now we do not have sufficient data to recommend any specific class of glucose-lowering drug products or their combination in terms of their effect on prevention of complications. Therefore, it would be justified to evaluate and compare glucose-lowering drug products and their combination predominantly in terms of their ability to reduce and maintain HbA1c and in terms of their safety, specific adverse effects, tolerability and convenience" [6]. The document further focuses on the special role of insulin in DM therapy, justifying it by the fact that insulin is the most potent antidiabetic agent; timely initiation of insulin therapy ensures optimal glycemic control and, consequently, improves type 2 DM prognosis delaying development of irreversible changes. Intensive insulin therapy proved to prevent vascular diabetic complications. With diabetes progression it becomes more difficult to manage, and insulin provides additional advantages since its effect is independent of residual secretory activity of beta-cells [4].

Materials and methods

Study design – retrospective, modeling. Methods of pharmacoeconomic analysis - cost-effectiveness, cost-utility. Modeling horizon – 1 year. Alternatives compared – insulin aspart (NovoRapid®), insulin lispro (Humalog®), insulin glulisine (Apidra®), premix insulin aspart 30/70 (NovoMix® 30), premix insulin lispro 25/75 (HumalogMix® 25), insulin detemir (Levemir®) and insulin glargine (Lantus®). Innovator drugs were compared in this study since they were used in randomized controlled studies (RCS) analyzing efficacy.

Efficacy analysis

Information search was performed to evaluate efficacy of therapeutic schemes compared. A number of studies were selected comparing insulin analogues in terms of their ability to reduce glycosylated hemoglobin and in terms of safety associated predominantly with the frequency of hypoglycemic episodes, specific adverse complications and effect on body weight of the subjects.
The studies performed by Niskanen et al. and Hermansen et al. [5, 6] compared premix insulin analogues: aspart 30/70 and lispro 25/75. In the study by Niskanen et al. insulin doses were titrated until optimal blood glucose levels were achieved. Average daily insulin dose was identical in both groups. The study did not reveal statistically significant differences in HbA1c level decrease. Hermansen et al. used similar insulin doses based on the subjects' body weight; however, they evaluated

Kulikov A.Yu. - mob: (926) 800-10-56, e-mail: 7677041@mail.com

only postprandial glucose level; reduced values were not statistically different between the groups. The number of hypoglycemic episodes and body weight changes was also similar between the drugs in both studies.

Meta-analysis by Canadian Agency for Drugs and Technologies in Health [7] compared short-acting insulin analogues (aspart and lispro) with human insulin. Six RCS were selected to compare human insulin and aspart involving 1031 subjects. To compare lispro insulin and human insulin, 11 studies were analyzed enrolling 3031 subjects. No statistically significant differences were reported between the groups in terms of HbA1c reduction, incidence of severe hypoglycemic episodes and body weight changes. Two studies included into meta-analysis demonstrated reduced overall hypoglycemic episodes when comparing insulin aspart (NovoRapid®) and short-acting human insulin (RR 0.72 (0.64, 0.80)). Three studies also indicated statistically significant reduction in the incidence of nocturnal hypoglycemia when comparing lispro insulin and human insulin (RR 0.58 (0.48, 0.70)).

Meta-analyses by George Dailey et. al. and Swinnen S.G. et. al. [8, 9] revealed no statistically significant differences in HbA1c level decrease or incidence of hypoglycemic episodes between the groups receiving long-acting insulin analogues (detemir and glargine); however, higher daily doses of insulin detemir were required vs. insulin glargine.

Therefore, information search admitted that in terms of glycemic profile control and reduced level of glycosylated hemoglobin short-acting (aspart, lispro), premix (aspart 30/70, lispro 25/75) and basal (detemir, glargine) insulin analogues have comparable therapeutic efficacy within each group. Due to lacking comprehensive evidence for insulin glulisine it was considered as equally effective vs. other short-acting insulins examined in this analysis. However, to assess efficacy of therapeutic schemes, information search provided one study comparing short-acting insulin analogues with basal and two-phase analogues for type 2 DM therapy.

An open-label, controlled, multicenter study carried out by Rury R. Holman et.al. [10] enrolled 708 subjects with suboptimal average glycosylated hemoglobin level HbA1c = 8.5 adminestering maximum tolerated doses of metformin and sulfonylurea who used additionally premix aspart insulin (NovoMix® 30) twice daily, short-acting insulin aspart (NovoRapid®) three times daily or basal insulin detemir (Levemir®) once or twice daily as required. The endpoints after 1 year after the study initiation were average glycosylated hemoglobin level, number of subjects with glycosylated hemoglobin below 7.0% and 6.5%, incidence of hypoglycemia and increased body weight. Proportion of subjects with HbA1c < 7% was 48.7%, 41.7% and 27.8%, while the total incidence of hypoglycemia was 12; 5,7 and 2.3 events per patient-year for short-acting insulin aspart (NovoRapid®), premix insulin aspart (NovoMix® 30) and basal insulin detemir (Levemir®), respectively. Since this study did not reveal any relevant data concerning the incidence of severe hypoglycemia, the present analysis used the values from the studies for each of the alternative therapies compared (table 1).

Utility assessment

Cost-utility analysis used integral QALY value. To calculate total QALY, utility values were used throughout the whole modeling period for each condition of the subject within a certain period. Various levels of utility are associated with adverse effects, hypoglycemic conditions and body weight gain.

To evaluate the total quality of life of the subjects with DM type 2 and related ischemic disorders and body weight gain, utility values per one-year treatment were used.

For conditions such as moderate or severe hypoglycemia and gastrointestinal pain arising at a certain period of time, QALD value was used which was calculated using the formula:

$$QALD'S(State) = R\%^* n^*Utility, \text{ where}$$

QALD'S(State) – the number QALD'S obtained during a certain condition;
R% - incidence of the condition;
n – duration of the condition in days;
Utility – utility associated with such condition.

After calculating QALD'S for each condition, these values are summarized. The final QALD'S value divided by the number of treatment days yields QALY value. Table 2 presents utility values for all conditions.

Таблица 2. Значения полезности в модели

Condition	Utility
DM type 2	0,8[a]
body weight gain by 1 kg	-0,036[b]
ischemic disorders of coronary arteries	-0,037[c]
severe hypoglycemia	-0,549[a]
moderate and mild hypoglycemia	-0,0017[a]
gastrointestinal pain	-0,0036[d]

[a] - according to PE study by Chris G. Cameron et.al. [13]. It should be noted that to calculate utility value of moderate hypoglycemia episode, recalculation was made since the study in question specifies that the episode decreases utility value by 0.167 for 15-min period making 0.0017 units per day.

[b] – the study by Hoerger TJ et.al. [14] demonstrated increased utility value by 0.0899 against BMI reduction by 1. Based on the baseline characteristics of the subjects in the study by Rury R. Holman et.al. [10] (average body weight – 85.8 kg, BMI – 29.8) yielding the results for efficacy analysis, it was established that BMI increase by 1 is associated with body weight gain by 2.5 kg on average. Therefore, reduced utility value against body weight gain by 1 kg was 0.036.

[c] - quality of life data were taken from the study by Oddvar Solli et.al. in which EuroQoL (EQ-5D) questionnaire was used [15].

[d] – data were taken from the study by R. A. Elliott et. al. [16], at that utility data is presented for the whole 10-day adverse effect period.

Table 1. Efficacy analysis results

	Short-acting insulin (NovoRapid)	Two-phase insulin (NovoMix 30)	Basal insulin (Levemir)
Hba1 < 7 (% subjects)[a]	48,70	41,70	27,80
Incidence of moderate hypoglycemia (cases per patient-year)[a]	12,00	5,70	2,30
Incidence of severe hypoglycemia (cases per patient-year)	0,05[b]	0,01[c]	0,003[c]
Increased body weight (kg)[a]	4,7	5,7	1,9
Incidence of ischemic disorders (cases per patient-year)[a]	0,017	0,013	0,013
Incidence of GI symptoms (cases per patient-year)[a]	0	0,017	0

[a] – according to study performed by Rury R. Holman et.al. [10]

[b] – according to study performed by George Dailey et.al. [11]

[c] – according to study performed by John B. Buse et.al. [12]

Cost analysis

Data concerning the cost of the medicinal products compared were taken from the State register of the limit selling prices of manufacturers and limit retail prices for the medicinal products referred to the list of vital and essential medicines (as of September 01, 2013) [17], at that limit prices with VAT included were used. Dosing information and the data concerning amount and cost of healthcare resources used by default were obtained according to medical assistance standards for the subjects with diabetes mellitus [18]. Cost of medical services was taken from the pricelist of Endocrinological Research Center for commercial medical services (as of 2013) [19]. Cost analysis for the disease was represented by calculation of direct costs of type 2 DM therapy for each of the medicinal products compared including the costs for therapy with the medicinal products compared and costs for medical procedures. Table 3 contains the cost of therapy with the medicinal products included into the schemes compared.

Table 3. Results of cost analysis of the compared medicinal products per one subject/year, rub.

Drug	Cost of insulin therapy	Total costs
NovoRapid®	11916,57	53172,60
Humalog®	13947,87	55203,90
Apidra®	15979,80	57235,83
NovoMix® 30	17894,27	59150,30
HumalogMix® 25	21797,80	63053,83
Levemir®	16689,94	57945,97
Lantus®	27444,20	68700,23

Cost, efficacy and utility results

The following stage of the study included cost-efficacy analysis.
The value reflecting proportion of subjects with HbA1c<7% was used as efficacy criterion for cost- efficacy analysis in this study.
Cost- efficacy value was calculated using the formula:

CER= Cost/Eff, where

CER – cost- efficacy ratio
Cost – total costs of therapeutic scheme compared (rub.);
Eff – efficacy value expressed as % proportion of subjects with HbA1c<7%
The result of cost- efficacy analysis demonstrated that the lowest CER belongs to NovoRapid®, the highest – to Lantus® (Fig. 1).

Cost-utility ratio was calculated using the formula:

CUR= Cost/QALY, where:

CUR – cost-utility ratio
Cost - total costs of therapeutic scheme compared (rub.);
QALY – incremental utility value reflecting the number of quality adjusted life years

Cost-utility analysis demonstrated that the lowest CUR value belongs to NovoRapid®, the highest – to Lantus® (Fig. 2).

Results of cost- efficacy and cost-utility analyses are presented in table 4.

Figure 1. **Results of cost-efficacy analysis**

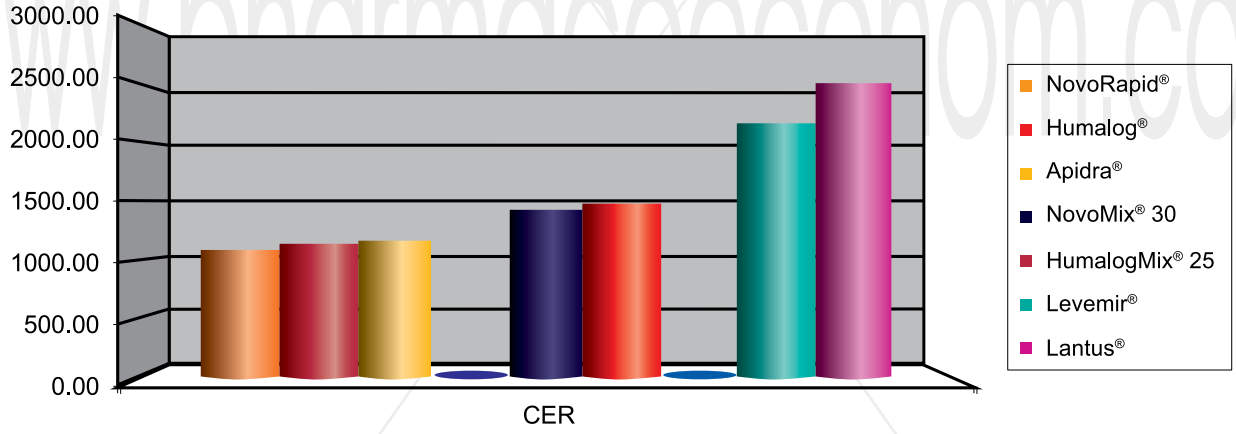

Figure 2. **Cost-utility analysis results**

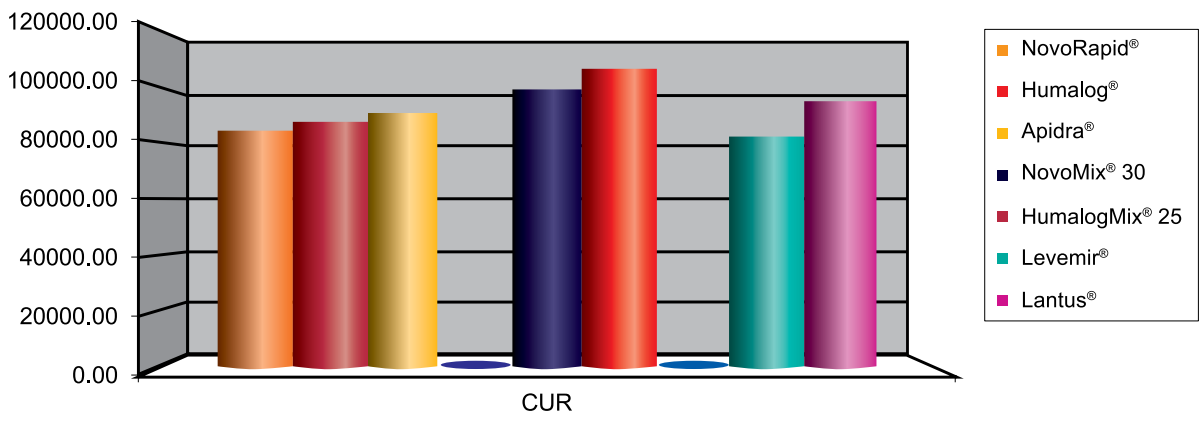

Table 4. Results of cost- efficacy and cost-utility analyses

Drug	Total costs, rub.	HbA1c < 7%	QALY	CER (rub.)	CUR (rub.)
NovoRapid®	53172,60	48.7	0,6295	1091,84	84463,04
Humalog®	55203,90	48.7	0,6295	1133,55	87689,69
Apidra®	57235,83	48.7	0,6295	1175,27	90917,35
NovoMix® 30	59150,30	41.7	0,5940	1418,47	99573,21
HumalogMix® 25	63053,83	41.7	0,5940	1512,08	106144,38
Levemir®	57945,97	27.8	0,7310	2084,39	79269,45
Lantus®	68700,23	27.8	0,7310	2471,23	93981,16

Conclusions

Cost analysis indicated that when adding insulin analogues to OAD therapy the lowest cost belongs to NovoRapid® (53172.60 rub.), the highest – to Lantus® (68700.23 rub.) associated with high cost of the drug.

According to cost- efficacy analysis, the lowest CER value is typical for NovoRapid® (1091.84 rub.), the highest – for Lantus® (2471.23 rub.). However, interpretation of cost- efficacy analysis results should take into account that efficacy expressed in the number of subjects reaching target level of glycosylated hemoglobin (HbA1c < 7%) does not differ between the medicinal product groups (short-acting, premix and basal insulin analogues). Considering therapeutic standards for each drug group in the absence of reaching various target HbA1c levels, it would be reasonable to evaluate the results of cost- efficacy analysis within each group on an individual basis.

Among short-acting insulin analogues CER value was 1091.84 rub.; 1133.55 rub. and 1175.27 rub. for NovoRapid®, Humalog® and Apidra®, respectively.

Among premix insulin analogues CER was 1418.47 for NovoMix® 30 and 1512.08 rub. for HumalogMix® 25.

Among basal insulin analogues CER value was 2084.39 rub. for Levemir® and 2471.23 rub. – for Lantus®.

Therefore, in terms of cost-efficacy, when short-acting, premix and basal insulins were added to OAD treatment, NovoRapid®, NovoMix® 30 and Levemir® are the preferable drug products, respectively.

Cost analysis and cost-efficacy analysis demonstrated advantages of short-active and premix insulins over basal ones; however, when target HbA1c levels are achieved using basal insulin analogues, their use is recommended according to cost-utility analysis.

CUR value for NovoRapid®, Humalog®, Apidra®, NovoMix® 30, HumalogMix® 25, Levemir® and Lantus® was 84463.04 rub., 87689.69 rub., 90917.35 rub., 99573.21 rub., 106144.38 rub., 79269.45 rub. and 93981.16 rub. for 1 QALY, respectively.

The lowest CUR belonged to NovoRapid®. Therefore, in terms of cost-utility analysis, when insulins were added to OAD treatment, NovoRapid® was the preferential preferable drug product. Among premix and basal insulin analogues, NovoMix® 30 and Levemir® were preferential drugs as the ones having the lowest CUR values in the relevant groups.

References:

1. Sountsov Yu. I., Dedov I. I.: The State Register of Diabetec Patients – the main information system calculating and planning the state economic spending on Diabetes. Sakharny Diabet N2, 2005
2. IDF Diabetes Atlas 5th edition, 2012 update © International Diabetes Federation, 2012
3. Rehan Qayyum, M.D., Lisa M. Wilson, Sc.M., Shari Bolen, M.D., M.P.H. Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes. Comparative Effectiveness Review- 2008, No. 14
4. AACE/ACE Consensus Statement, Glycemic Control Algorithm, Endocr Pract. 2009;15(No. 6) 545
5. Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther 2004; 26(4):531-40.
6. Hermansen K, Colombo M, Storgaard H, OStergaard A, Kolendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care 2002; 25(5):883-8
7. Khai Tran, MSc PhD, Srabani Banerjee, MSc PhD, Huimin Li, MA. Rapid-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes. CADTH Technology Overviews, Vol. 1, 2010
8. George Dailey et. al. Relationship of Insulin Dose, A1c Lowering, and Weight in Type 2 Diabetes: Comparing Insulin Glargine and Insulin Detemir. DIABETES TECHNOLOGY & THERAPEUTICS. Volume 12, Number 12, 2010: 1019 – 27.
9. Swinnen S.G. et. al. Insulin detemir versus insulin glargine for type 2 diabetes mellitus (Review). This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2011, Issue 7.
10. Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc., Andrew J. Farmer, D.M., F.R.C.G.P.. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med 2007;357:1716-30
11. George Dailey, MD, Julio Rosenstock, MD, Robert G. Moses. Insulin Glulisine Provides Improved Glycemic Control in Patients With Type 2 Diabetes. Diabetes Care 27:2363–2368, 2004
12. Hans U. Janka, MD, Gerd Plewe, MD, Matthew C. Riddle. Comparison of Basal Insulin Added to Oral Agents Versus Twice-Daily Premixed Insulin as Initial Insulin Therapy for Type 2 Diabetes. Diabetes Care 28:254–259, 2005
13. Chris G. Cameron MSc, Heather A. Bennett BPharm PhD. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ 2009;180(4):400-7
14. Thomas J. Hoerger, Phd, Ping Zhang, Phd, Joel E. Segel, Ba. Cost-Effectiveness of Bariatric Surgery for Severely Obese Adults With Diabetes. Diabetes Care 33:1933–1939, 2010
15. Oddvar Solli, Knut Stavem, IS Kristiansen. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. Health Qual Life Outcomes. 2010; 8: 18
16. R. A. Elliott, L. Hooper, K. Payne. Preventing non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: are older strategies more cost-effective in the general population? Rheumatology 2006;45:606–613
17. State register of the limit selling prices of manufacturers and limit retail prices for the drugs referred to the list of vital and essential medicines (as of 01.09.2013)
18. Decree of the RF MoH "Medical assistance standards for the subjects with diabetes mellitus" dated January 18, 2013.
19. http://www.endocrincentr.ru/pacient/price/